EX·LIBRIS·COLL·MED·PHILAD·INSTIT·A·D·MDCCLXXXVII.
NON SIBI SED TOTI

Class _____ No. Journal

LIBRARY GENERAL FUNDS

Luther S. Bent
Binding Fund
William T. Carter
Catalogue Endowment
Louis A. Duhring
W. V. & J. M. Keating
Henry Leffman
Library Endowment
Morris Longstreth
Phila. Med. Society
Charles H. Vinton
Douglas Stockton Warren
J. William White
Caspar Wistar

Bdg. 3.05

LIBRARY OF THE
COLLEGE OF PHYSICIANS
OF PHILADELPHIA

Digitized by the Internet Archive
in 2013

http://archive.org/details/transactionsstud4281coll

TRANSACTIONS & STUDIES

of the

College of Physicians

of

Philadelphia

FOURTH SERIES

VOLUME 28

1960–61

WAVERLY PRESS, INC.
Baltimore, Md.

The College of Physicians of Philadelphia does not assume responsibility for statements or views expressed by contributors to the *Transactions & Studies*. The editor checks bibliographic references, to aid in making them factually reliable, and occasionally supplies headings in the text, to facilitate reference to clearly defined portions of the text; the communications are in other respects printed exactly as they were submitted, subject to author corrections on the galleys.

An index to the annual volume of the *Transactions & Studies* appears in the fourth and final (April) number of the volume.

The communications pertinent to their respective fields are indexed in: *Biological Abstracts; Chemical Abstracts; Index Medicus.*

The Transactions & Studies of the College of Physicians of Philadelphia is published four times a year—July, October, January, April—at Baltimore, Maryland by the College of Physicians of Philadelphia. Subscription, $5.00 a volume. Single copies, $1.25.
Publication Office: Mt. Royal and Guilford Aves., Baltimore 2, Md. *Editorial correspondence* should be addressed to: The Editor, College of Physicians of Philadelphia, 19 South 22d Street, Philadelphia-3, Pa. Entered as second class matter June 21, 1938, at the Post Office at Baltimore, Md., under the act of August 24, 1912.
Printed in U. S. A.

Contents

NO. 1, JULY 1960

Visualization of Cellular Events in the Healing of Burns (*Mary Scott Newbold Lecture LXXVIII*) CHARLES M. POMERAT 1

The Nature of Polymyositis and Related Muscular Diseases (*Hira S. Chouké Lecture III*) DEREK DENNY-BROWN 14

The Use of Enzymes for Therapy (*Nathan Lewis Hatfield Lecture XLIV*) ..... WILLIAM S. TILLETT 30

Tranquilizers: Their Use and Abuse (*William Harvey Perkins Prize Essay I*) ..... CYRIL F. CONWAY, JR. 38

Mark Akenside: Eighteenth Century Physician-Poet ..... HERBERT J. DIETRICH, JR. 46

Memoirs

William C. Stadie (1886–1959) ..... ISAAC STARR 50

Edward A. Strecker (1887–1959) ..... KENNETH E. APPEL 52

Frank Ardary Craig (1876–1959) ..... JOHN B. FLICK 54

Edward Welles Bixby, Sr. (1887–1959) ..... T. GRIER MILLER 57

Frederick Fraley (1876–1959) ..... JESSE T. NICHOLSON 58

NO. 2, OCTOBER 1960

The Etiology of Human Liver Cancer in Africa and the United States of America (*Thomas Dent Mütter Lecture LXXII*) ..... PAUL E. STEINER 61

A Consideration of the Mechanisms of Resistance to Viral Infection Based on Recent Studies of the Agents of Measles and Poliomyelitis (*James M. Anders Lecture XXXIX*) ..... JOHN F. ENDERS 68

The Unicorn in Medical History (*Kate Hurd Mead Lecture XII*) ..... GENEVIEVE MILLER 80

A Guide to Health—An Epistle to a Friend (Thomas Jefferson) by Charles Willson Peale FRED B. ROGERS 94

Memoirs

Joseph D. Aronson (1889–1958) ..... ESMOND R. LONG 100

Patrick A. McCarthy (1884–1959) ..... HUGH ROBERTSON 103

Charles Leonard Brown (1899–1959) ..... THOMAS M. DURANT 104

Edward Weiss (1895–1960) ..... O. SPURGEON ENGLISH 106

NO. 3, JANUARY 1961

Observations and Reflections on the Lymphatic System (*Mary Scott Newbold Lecture LXXX*) H. S. MAYERSON 109

Philadelphia Doctors in the White House (*Edward Bell Krumbhaar Prize Essay III*) ..... DEAN ARVAN 128

Observations of a Pilot "Health Education Center" in a New-Immigrant Town in the Upper Galilee (*William Harvey Perkins Prize Essay II*) ..... NAOMI R. BLUESTONE 135

Community Health Interests of Temple University Medical Center VICTOR J. LOCICERO AND WILLIAM A. STEIGER 141

Memoirs

William Warder Cadbury (1877–1959) ..... S. EMLEN STOKES 144

Israel Pemberton Pleasants Hollingsworth (1880–1960) ..... HENRY PLEASANTS, JR. 146

George Morrison Coates (1874–1960) ..... HARRY P. SCHENCK 147

AUG 17 1961

NO. 4, APRIL 1961

President's Address ..... JONATHAN E. RHOADS 149
Inaugural Remarks ..... THOMAS M. DURANT 154
Two Landmarks in American Medicine—Their Impact ..... TRUMAN G. SCHNABEL 156

Memoirs

Charles Howard Miner (1868–1959) ..... GEORGE MORRIS PIERSOL 164
Louise Pearce (1885–1959) ..... MARION S. FAY 167
William Daniel Stroud (1891–1959) ..... CHARLES C. WOLFERTH 169
Myer Solis-Cohen (1877–1960) ..... JESSE T. NICHOLSON 171
David Nathaniel Kremer (1890–1960) ..... TRUMAN G. SCHNABEL 173
George N. J. Sommer, Sr. (1874–1960) ..... I. S. RAVDIN 174

Annual Reports

Treasurer, 175; Library, 179; Mütter Museum and College Collections, 188.
Census of Incunabula in the College Library, Supplement I, 1960 191
Transactions of the Sections: Programs and Abstracts from the Section on General Medicine 193
List of College Lectures, 1960 223
Officers, Committees, Sections, and Administrative Staff of the College, 1961 224
List of Fellows 228
Suggested Form of Bequest 252
Index to Volume 28 253

TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Volume 28 (Fourth Series)

Number 1 (July 1960)

Visualization of Cellular Events in the Healing of Burns[1]

By CHARLES M. POMERAT, PH.D.[2]

THIS project was concerned with a description of cellular activities in the repair of burns on the basis of what can be seen following the explantation of tissues at various stages in the process as studied with the aid of phase contrast, time-lapse cinematography.

The goals of the enterprise included observations of fundamental interest in cytology such as the genetic relations of cell types, the phenomenon of "modulation", and the role of connective tissue elements in the formation of acellular materials. From the more practical point of view, film records of cellular dynamics might prove useful for a better understanding of the rationale in the modern management of burns or, at least, in the teaching of accepted therapeutic practices to medical students and military surgeons.

Essential to the project was a chronological classification of the major events which take place following third degree burns until complete repair is achieved. This was provided by Dr. T. G. Blocker, Jr. and his associates who also made tissue and clinical data available for the study. The four major stages of repair and their subdivisions are:

Stage I	1) Immediate
	2) Reactive (dry) non-suppurative
Stage II	1) Suppurative (dry)
	2) Granulating (dirty)
	3) Granulating (clean)
	4) Granulating (late)
	a. boggy
	b. firm
Stage III	1) Grafted
	2) Healed (early)
Stage IV	1) Healed (reactive)
	2) Normal

[1] Mary Scott Newbold Lecture LXXVIII, College of Physicians of Philadelphia, 4 November 1959.

[2] Professor of Cytology and Director of the Tissue Culture Laboratory, Department of Anatomy, University of Texas—Medical Branch, Galveston, Texas.

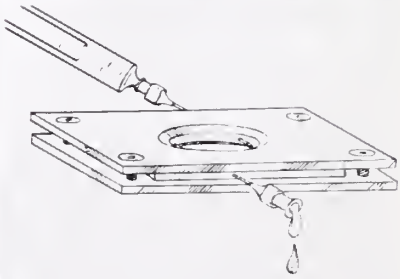
Note: This lecture was illustrated with approximately 60 lantern slides and a 1000′ reel of 16 mm. film. In the interest of economy and by way of recording a section of previously unpublished material, this paper is limited to aspects of wound healing. An appreciation of "cytology in action" is difficult to render on the printed page, but selected film frames have been abstracted from the records to convey some impression of mobility manifestations of human reparative cells in vitro.

This work was supported by Contract DA-49-007-MD-32, U. S. Army Medical Research and Development Command, Office of the Surgeon General.

1

2

3



ROSE CHAMBER

4

While many preliminary studies were done on several patients treated for burns to assure the adequacy of our methods, the results reported here concern more detailed observations on two subjects (W. G. and L. P., Figs. 1 and 2). Concentrated effort centered on the accumulation of data for Stage II, 2—Granulation (dirty), Stage II, 3—Granulation (clean), and the secondary firm type of granulation described in our scheme of classifications as Stage II, 4b. Attention was also directed at establishing the feasibility of setting up programs for studying (1) conjoint cultures of granulation tissue and epidermal explants; (2) the interplay between granulating cells, bacteria (*Proteus vulgaris* and *Pseudomonas aeruginosa*) and antibiotics; (3) the effect of electrolytes on the elements of granulation; (4) the possibility that low dosages of gamma radiation might stimulate reparative elements; and (5) the advisability of preparing a teaching film on the management of wounds on the basis of dynamic cytology.

OBSERVATIONS

A. *Granulation tissue associated with active suppuration* (Stage II, 2).

This was obtained from a 36-year-old white male (W. G.) with a 47% body surface burn. The area at the base of the right arm from which tissue was removed for explantation is shown in Figure 1. Cultures set up in Rose (1) chambers (Fig. 4) and maintained at 37°C. were photographed immediately following the addition of the feeding solution with the use of phase contrast cinematography at very low magnification (3.5 or 5× objective and no ocular). Film records were generally made at one frame per minute (1 f. m.) for 3 to 5 days with the use of a cine unit shown in Figure 3. These not only showed the dramatic outflow of polymorphonuclear cells, the activities of lymphocytes, monocytes, macrophages and spindle cells in an environment protected by both 1000 units of penicillin sodium G in the nutrient fluid and 1 mg. of neomycin of the plasma per ml., but permitted the selection of film frames suitable for the analysis of the time course of various processes.

Selected frames (Figs. 5–10) from a film sequence showed a dominance of heterophiles in emigration during the first 10 hours of incubation. As is well known, such cells show progressive degeneration and death by the 5th or 6th day in vitro. These processes were recorded especially well at a moderate magnification over a period of 1 hour and 18 minutes to include details of the disorganization of the neutrophiles and the removal of their debris by phagocytic elements (Figs. 11–18). Microphages having ingested, and presumably digested, complex substances may serve as do the macrophages in the preparation of bodies endowed with the property described by the term *antigenicity*. Direct observations of what may be seen of this phenomenon in the living state are urgently needed.

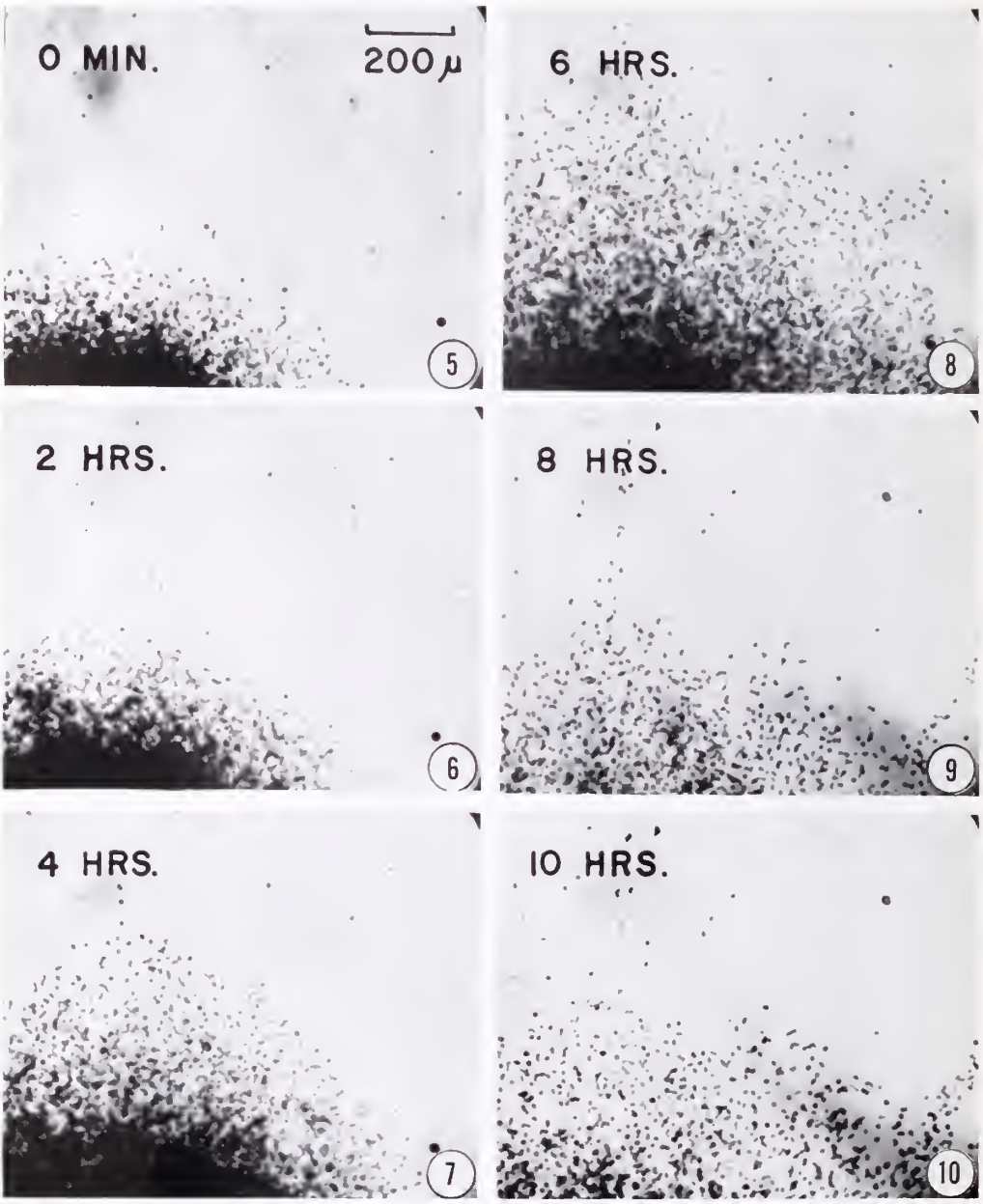
The term "polyblast of inflammation" which was introduced by Maximow was found useful in describing cells of variable mor-

FIG. 1. Granulating tissue associated with active suppuration was employed for tissue culture studies on the behavior of the cellular content of explants characteristic of this phase of wound healing (Stage II, 2). The patient was a 36-year old white male (W. G.) with a 47% body surface burn. A biopsy approximately 1 cm. square and 4 mm. thick was taken in the area indicated by the scalpel tip and employed to make millimeter square fragments for culture.

FIG. 2. Clean (Stage II, 3) and late, firm type (Stage II, 4b) granulating tissue. The patient (L.P.) was a 30-year old Negress with a more than 60% body surface burn. Tissue was removed from both of these areas and treated as described for the patient represented in Figure 1.

FIG. 3. Setup for time-lapse cinematography. A microscope with phase contrast optics is contained in an incubator maintained at 37°C. A periscope and a cine camera can be seen above the microscope with an illuminating system below. At low power film records were made at 1 frame per minute, while at higher magnifications rates of 4 and 8 frames per minute were employed.

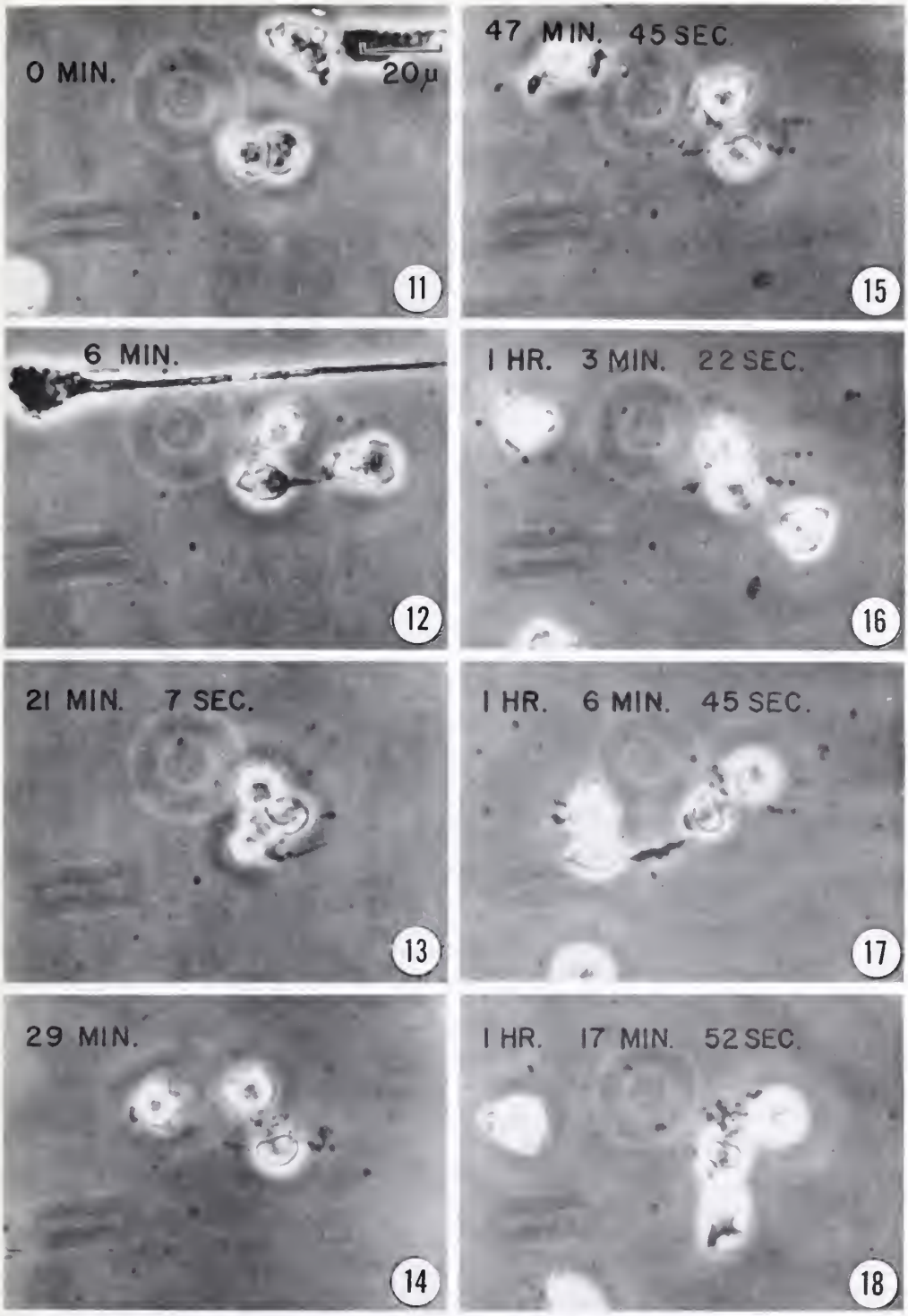
FIG. 4. Rose chamber. This sandwich type of container is formed with the use of a gum rubber or silicone gasket between two 43 × 50 mm. cover glasses of #1 thinness held firmly together by screws through two stainless steel or aluminum plates. Replenishment of nutrient fluid is easily achieved by introducing #25 gauge needles through the gasket after wiping its margin with alcohol.



FIGS. 5–10. Initial outgrowth from an explant of dirty granulating tissue (Stage II, 2) from patient W. G. (see Fig. 1). Film frames were selected from a cine record made at one frame per minute. The time is indicated on each photograph and the scale of magnification is given on the upper left figure.

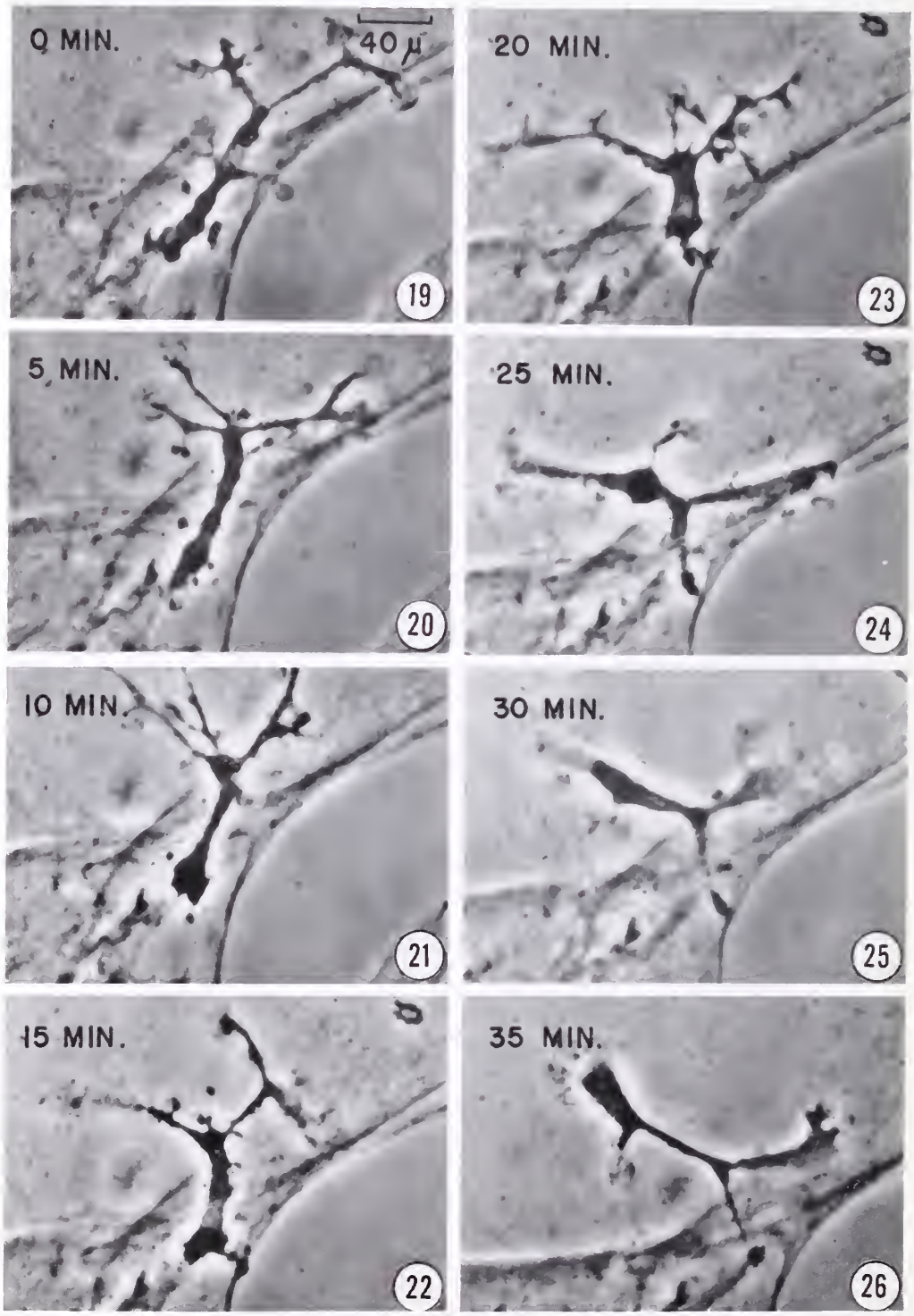
The majority of the cells were neutrophiles. After six hours when the field was nearly filled, the preparation was moved by means of the mechanical stage to permit continued recording of the outwandering cells.

phology but characterized by very active cytoplasmic membranes and an active participation in the process of micro-debridement. In this category we included elements primarily of bipolar type described by Ebert and Florey (2) from ear chamber preparations as "elongated" cells which were believed to have originated from monocytes. Analyses of par-



FIGS. 11–18. Activities of neutrophiles as seen in a film sequence of a 24-hour culture. The time is indicated on each photograph and the scale of magnification is given on the upper left figure.

Debris surrounding the cell in the lower central part of the frame made at 29 minutes indicates the death of a cell. Living neutrophiles appear to become engaged in ingesting the fragments. The film frame selected at 6 minutes shows an elongated monocyte which was crossing the field.



FIGS. 19–26. Activity manifestations of an "elongated cell" presumed to represent a monocyte. The time is indicated on each selected film frame enlargement and the scale of magnification is given on the upper left figure.

The form and movement of such cells closely resembled those described for microglia from the central nervous system.

ticular fields recorded on the 6th and 7th days did not produce evidence of mitoses in these cells. This is in substantial agreement with the views of F. Jacoby (3) but we feel that further studies are needed concerning this point. Figures 19–26 show membrane activity in an elongated cell during a 35-minute period which closely resembled those recorded for microglial cells from the human brain.

Lymphocytes persisted in cultures incubated for 15 days. Their structures and activities did not appear to differ from corresponding elements recorded during the early hours of cultivation. The well-known peculiarities of polarized and depolarized activities were recorded at various magnifications. Such film sequences were particularly suitable to illustrate the continuous activity of neutrophiles, the alternating migratory and rest phases of lymphocytes, and the relatively stationary performance of large macrophages as described in studies such as those of P. deBruyn (4).

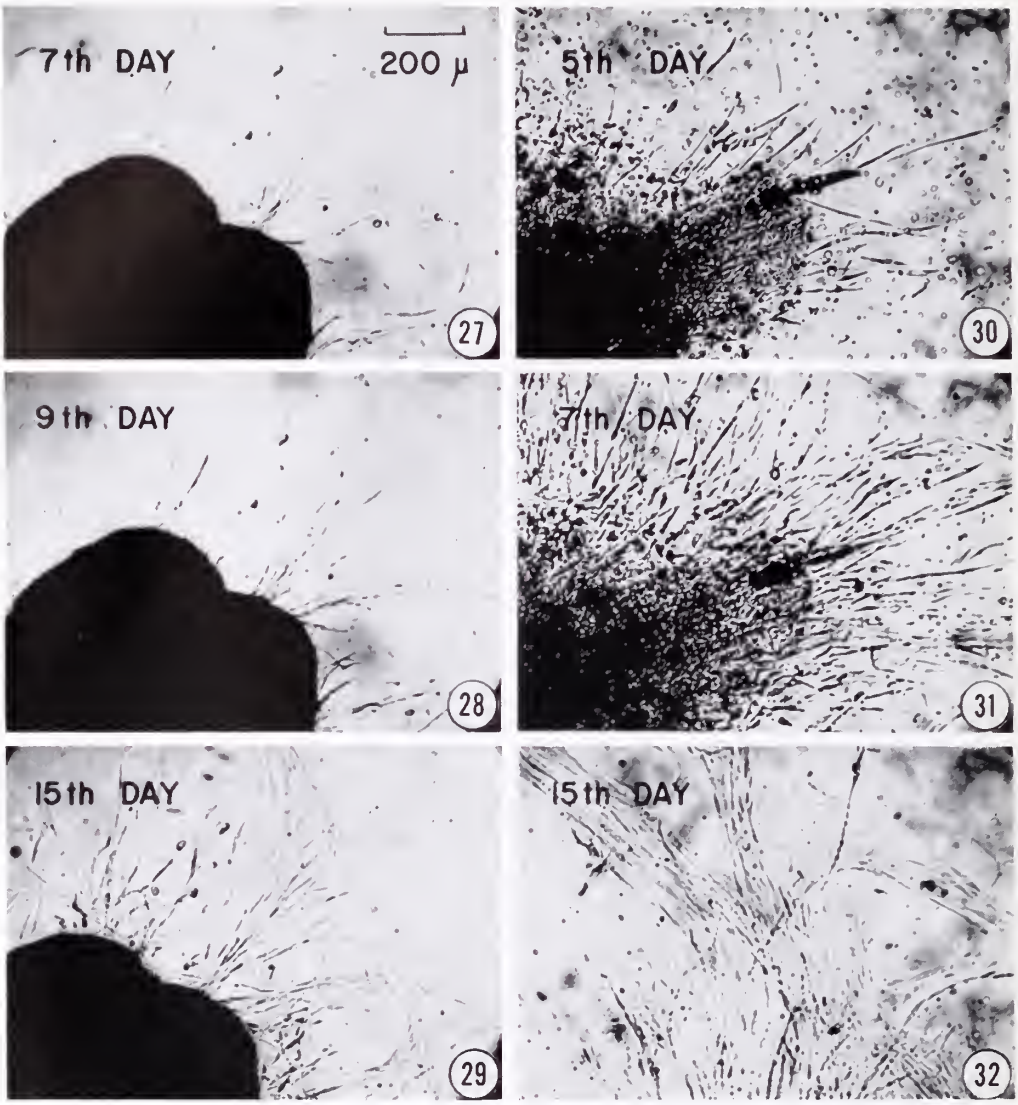
Spindle cell emigration generally observed on the 2nd day appeared to be delayed in cultures from septic tissues, but frequently under the influence of antibiotics the phase of neutrophilic death was followed by the proliferation of spindle cells to produce outgrowths resembling those observed in the cultivation of so-called clean granulation tissue.

B. *Late granulation tissue of the firm type* (Stage II, 4b).

The area from which this material was obtained was from the right leg of patient L. P., a 30-year-old Negress with a more than 60% body surface burn is shown in Figure 2. This consisted of a slightly elevated circular disc which had a firm consistency and light grey color as compared to the surrounding gelatinous, pink, vascular, clean granulating tissue. Records made for 2 or 3 days with cine photomicrography across a 20-day period of a particular explant showed delayed emigration of few spindle cells with rare accompanying leucocytes. The outgrowth as seen at several stages is shown in Figures 27–29. While the culture was practically free of neutrophiles, the paucity of migrating elements attested to the acellularity of the explant and probably to the firm association of fibers and ground substance. The contrast between the clean granulating material and the firm secondary tissue can be seen by comparing Figures 30–32 with Figures 27–29.

C. *Clean granulation tissue* (Stage II, 3) from patient L. P. (Fig. 2) was studied from explants obtained repeatedly during several weeks of her hospital stay. Such cultures showed a relatively small number of polymorphonuclear cells and monocytic derivatives as compared with those obtained from septic granulating tissue. While quantitative data are not yet available, the number of lymphocytes and macrophages appeared to be similar to those of explants from dirty wounds, at least after the 5th day of incubation under the aegis of antibiotics. Following a 2 or 3 day lag period, clean granulating tissue in vitro was characterized by a rapid increase in the population of spindle cells which could be accounted for by the large number of mitoses recorded in outwandering elements. While they are difficult to describe with static images abstracted from the cine record, one of the striking features of spindle cells in bands consisted of their gliding movement. The mechanism involved in this phenomenon has been reported by Dr. Paul Weiss (5) to be very poorly understood.

The straps and interlacing bands which were frequently produced by spindle cells led to the suspicion that some, if not most, of these represented endothelial structures (Figs. 29 and 32). Actively mobile elements such as lymphocytes were frequently seen to follow the course of oriented spindle cells, but no evidence was found of canalized vascular structures in de novo formations. However, on the basis of experience with the cultivation of patent blood vessels from adult human rib marrow (6) and with hemangiomatous tissue studied in our laboratory by J. Gonzalez Ramirez (7), it is believed that the majority of the spindle cell networks such as those shown in Figure 32 represented the in vitro counterpart of the vascular sprouts common in the active phase of granulation.



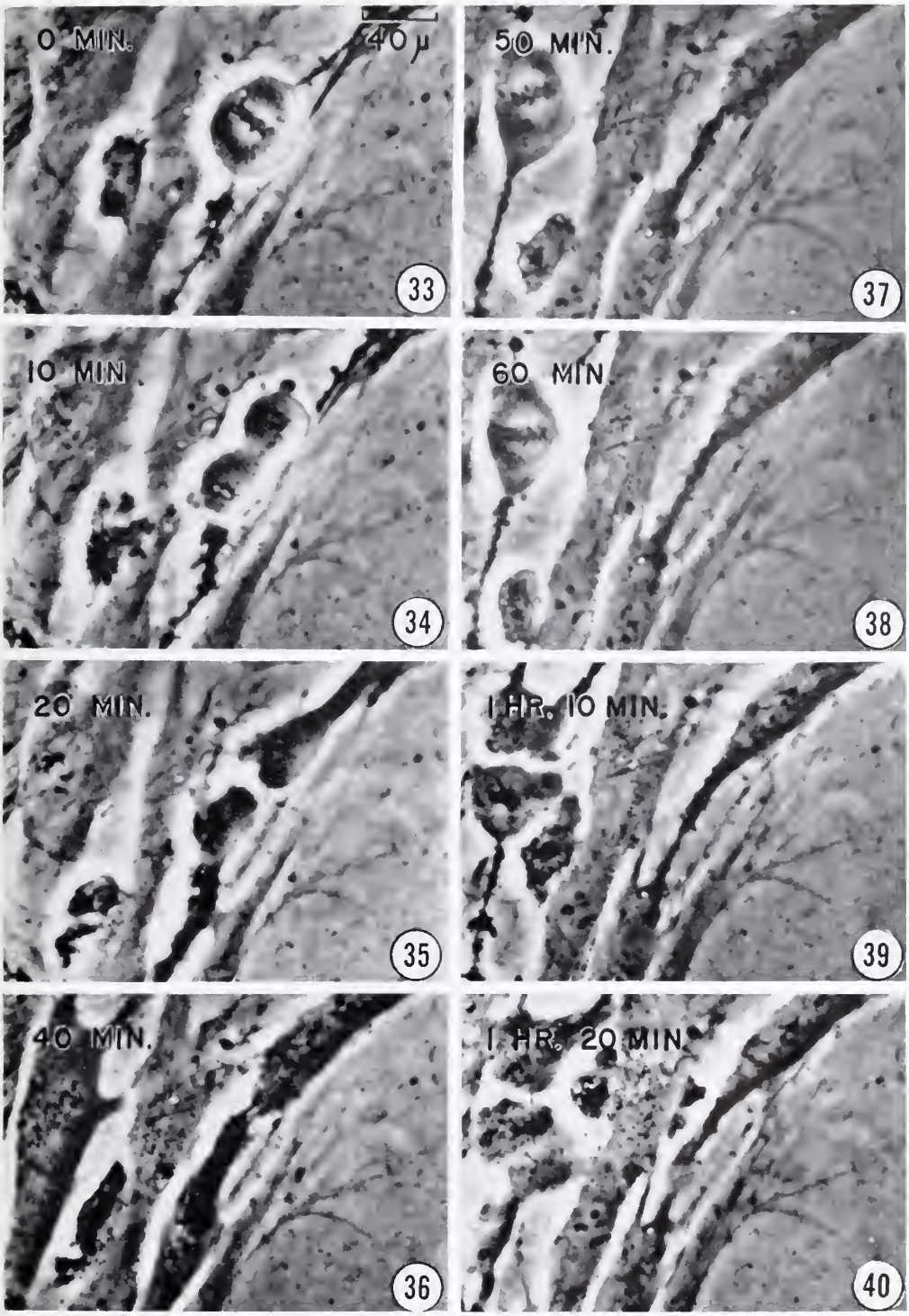
FIGS. 27–32. Comparison of outgrowth from secondary granulation tissue of the firm type (Stage II, 4b) on the left, with that obtained for clean granulating tissue (Stage II, 3) on the right half of the plate. Notice the paucity of cells from the secondary granulating tissue and the development of an abundant feltwork of spindle cells from tissue appropriate for the reception of skin grafts. The outgrowth in the lower right figure is suggestive of an endothelial formation.

Time relations are indicated on film frames and the scale for all frames is shown on the photograph at the upper left.

Figures 33–40 represent the division of a spindle cell. While this was in progress, another such element at the left-hand edge of the film frame entered prophase so that a complete record was obtained of mitosis in this species of cells. In the film projection, the activity of the membranes of the macrophage in the field suggests the role of these elements in what may be called micro-debridement.

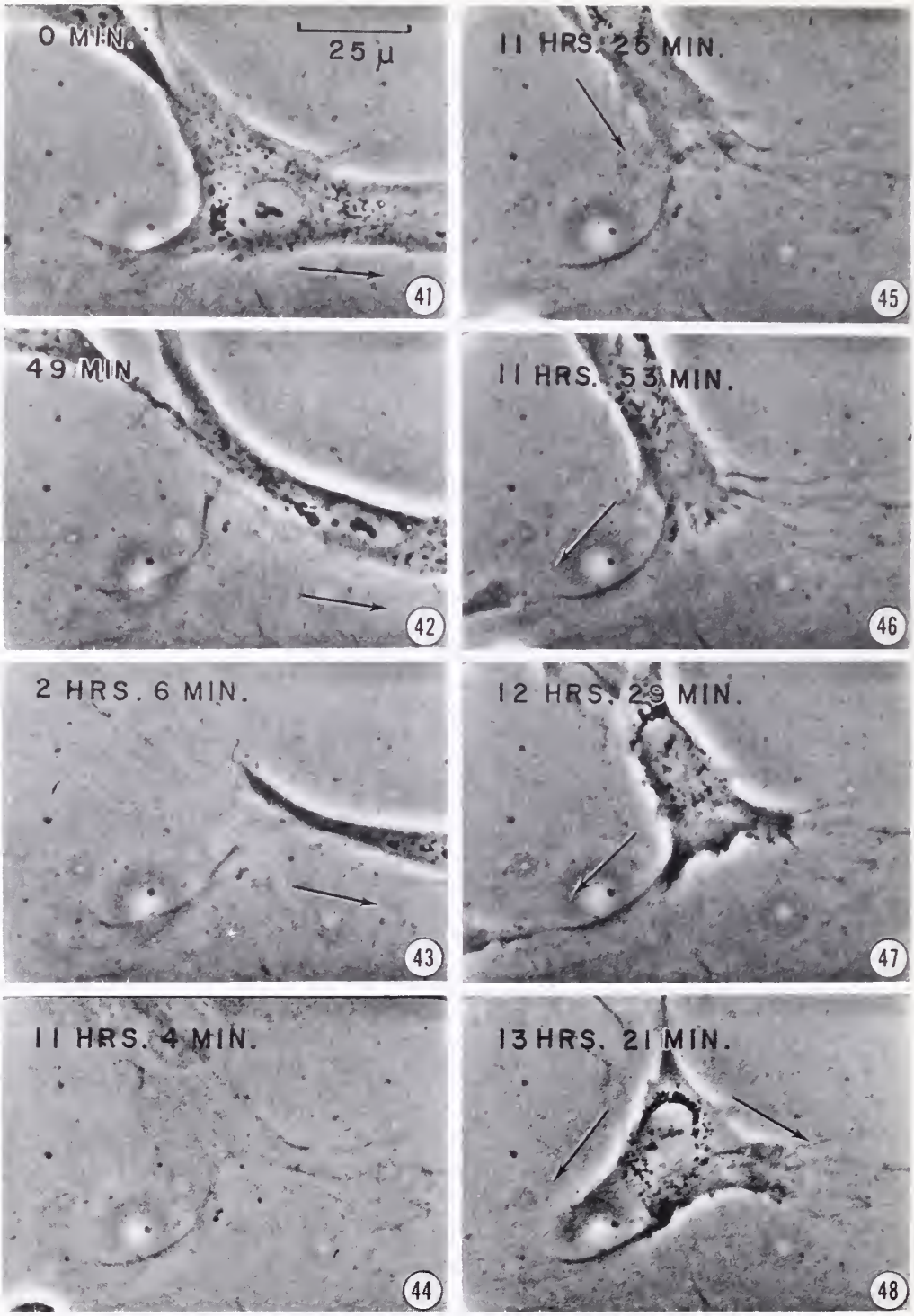
D. The genesis of acellular fibrillar materials.

One of the most unexpected and interesting results obtained with phase cinematography of human granulating tissue was the appearance



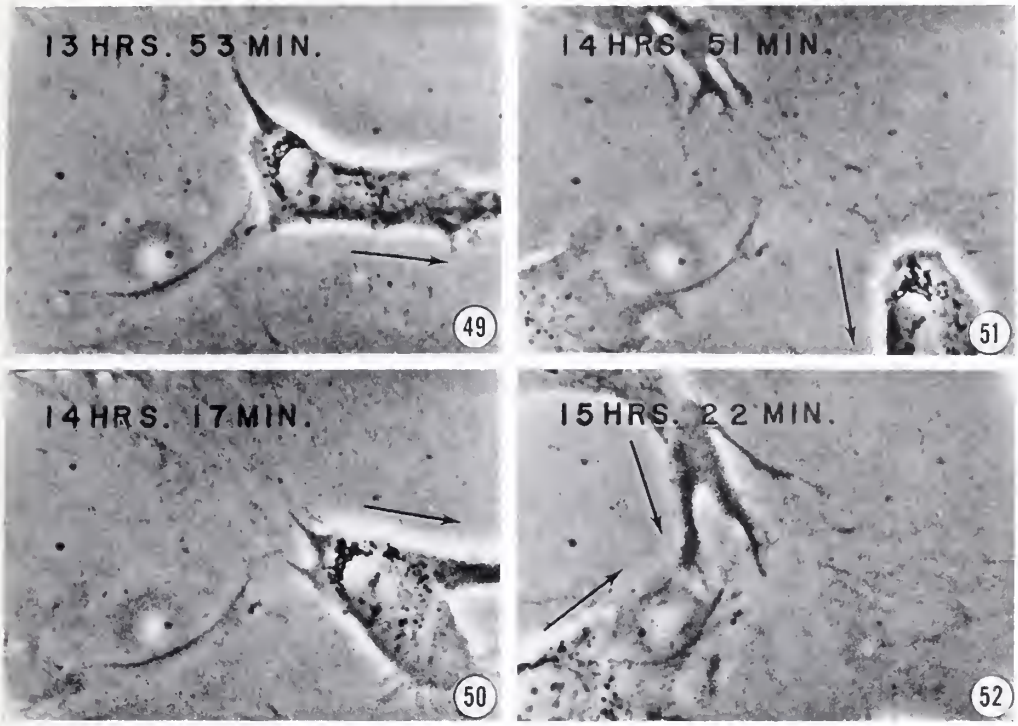
FIGS. 33–40. Proliferation of spindle cells in a 48-hour culture of granulating tissue. Mitosis is seen in two cells. A macrophage was actively engaged in what we believed to represent micro-debridement.

The time relations are indicated on each film frame and the scale of magnification is shown on the photograph at the upper left.



FIGS. 41–52. Acellular fibrillar materials in a 3-day culture of connective tissue from a clean granulating wound (Patient L.P.).

A delicate filigree (Fig. 44) which had formed in the wake of a slowly migrating stellate cell (Fig. 41) appeared to serve as a thigmotactic cue for the movement of a second element of fibroblastic type (Figs. 45–52). Two additional connective tissue cells entered the field (Fig. 51), presumably also orienting to acellular fibrillar structures. Arrows indicate the direction of cell movement.



Figs. 49–52

of very delicate fibrillar materials photographed at 1 frame per minute in a 3-day culture obtained from patient L. P. (Figs. 41–52). Numbers in the upper left areas of selected film frames represent the flight of time from the initially important portion of the record (Fig. 41). The large stellate cell in this field which was presumed to be a fibroblast moved to the right (arrow), disappearing completely after 11 hours and 4 minutes (Fig. 44). In its wake a delicate system of thread-like filaments remained, outlining the pattern of the original cell found in this field (compare Fig. 41 with Fig. 44). The membranous pseudopod of a cell destined to show a thigmotactic response to the filigree was seen to enter from the upper left margin of Fig. 44. The course of pseudopodal movements of this second element is indicated in Figures 45 to 52 by arrows. It will be observed that while the area of thread-like strands in the lower left quadrant were "explored," the major direction of the second cell was in the path of the first element to cross the field. In Figure 51 the pseudopodal extension of two other stellate elements are seen to enter the upper and lower left margins of the film frame.

Once having recognized the optical properties of acellular thread-like materials and the development of corresponding patterns from very delicate plasma membranes extended in the course of slowly migrating stellate cells, the analysis of activities in other sequences recorded from this culture reinforced the interpretation that we were dealing with the early phases of reticular fiber formation. These findings are in keeping with current observations by Moscona (8) on factors influencing the orientation of cells in the development of organotypic cultures from mixtures of trypsinized elements.

The genesis of connective tissue fibers, which has attracted much attention from electron microscopists, is a problem which cannot be reviewed within the scope of this lecture. The formation of argentophilic fibers de novo in

tissue culture has been the object of many reports. We have cooperated with Professor I. Costero and his associates at the University of Mexico in a series of studies (9, 10, 11) dealing with the demonstration of fibrillar materials in cell cultures with the use of metallic techniques. Intracellular proto-collagenous connective tissue fibrils demonstrated with the Rio-Hortega method tend to become pre-collagenous reticular fibers and later to produce collagenous bundles. Granulating tissue from extensive burns would seem to offer a rich source of experimental material both for basic studies on the genesis of connective tissue fibers in man as well as for investigations on a mechanism which unquestionably influences the future course of the epithelization of the wound surface.

DISCUSSION

In the recent history of tissue culture, much attention has been devoted to the study of so-called cell lines. In view of the very considerable achievements with their use in virology and for investigations in cell nutrition, the popularity of easily managed immortal strains of vertebrate elements is understandable. Our own group is finding the ease of obtaining quantitative data from a series of transformed human cells in continuous culture particularly valuable in chromosomal, radiobiological and pharmacological studies.

In the teaching of cytology and in the operation of laboratories dedicated to studies in the area of cell physiology with the use of in vitro methods, it is important to retain the eclectic position. The goals of certain investigations may require the use of rapidly multiplying cells of clone lines, but some projects may be defeated by a too great dependence upon such systems. The exciting achievements of students pursuing the chromosomal transformations which arise in the course of establishing cell lines should not exclude observations of deep biological interest which can be obtained in a few days with the use of primary explants. Buffy coat blood cell cultures currently are attracting students of human genetics. While the assessment of the differentiation of explanted peripheral and central neurons as represented by the de novo formation of Nissl substance, neurofibrils, and myelin is not easily plotted, the study of such phenomena as well as those involving complex cell interrelationships must not be neglected.

In a review of recent advances of tissue culture in cancer research, Dr. Margaret Murray (12) has issued a succinct warning: ". . . . Stimulating as is the demonstration that somatic vertebrate cells can behave like microorganisms, one must remind oneself that in so doing they are not behaving characteristically like vertebrate cells."

One of the nation's most distinguished students of morphogenesis, Dr. Paul Weiss (13) has called attention to the fact that ". . . Fascinating progress has been made in the study of some of the biochemical and biophysical components of the living system. But knowledge seems to have grown the faster, the smaller the sample of the living system that was taken under investigation. The major advances were made down at the molecular level. The task of dealing with the larger cellular level, therefore, involves a re-entry into areas of uncertainty . . . . The study of cells in interaction deflates complacent notions that all the major facets of cell life are truly understood even in principle."

My colleague, Dr. Donald Duncan, warns students that even in the face of notable achievements in cytochemistry and the extraordinary findings of electron microscopy, we are still in the Pre-Cambrian phase of cytological inquiry.

Perhaps it is fitting that this lecture on the complexities of cell behavior should close with a universally known passage of a local prophet: ". . . . And a mouse is miracle enough to stagger sextillions of infidels."

ACKNOWLEDGMENT

Grateful acknowledgment is made to Messrs. C. G. Lefeber and E. E. Pitsinger, Jr. for indispensable aid both with cine photographic recordings and their analyses.

REFERENCES

1. Rose, G.: A separable and multipurpose tissue culture chamber. Texas Rep. Biol. and Med. **12:** 1074–1083, 1954.
2. Ebert, R. H., and Florey, H. W.: Extravascular development of monocytes observed in vivo. Brit. J. Exper. Path. **20:** 342–356, 1939.
3. Jacoby, F.: In: *Wound Healing and Tissue Repair*, W. Bradford Patterson, Ed., University of Chicago Press, Chicago, 1959, p. 23.
4. de Bruyn, P. P. H.: The motion of the migrating cells in tissue cultures of lymph nodes. Anat. Rec. **93:** 295–315, 1945.
5. Weiss, Paul: Personal communication. 1956.
6. Woodard, W. C., and Pomerat, C. M.: The development of patent blood vessels from adult human rib marrow in tissue culture. Anat. Rec. **117:** 663–684, 1953.
7. Gonzalez Ramirez, J.: Contribucion al conocimiento de los hemangiomas. (Conceptos histopatológicos. Comportamiento en cultivo de tejidos). Bol. Inst. de Est. Med. y Biol., UNAM, XII: 113–145, 1954.
8. Moscona, A. A.: Personal communication. 1959.
9. Costero, I., Barroso-Moguel, R., Pomerat, C. M., and Chevez, A.: Caracterizacion del Sistema Fibroblastico. II. Fibrogenesis intracelular en tejido conectivo cultivado. Arch. Inst. Cardiol. de Mex., **24:** 337–372, 1954.
10. Costero, I., Barroso-Moguel, R., Chevez, A., and Pomerat, C. M.: Caracterizacion del Sistema Fibroblastico. IV. Fibrocitos reticulares. Arch. Inst. Cardiol. de Mex., **24:** 539–561, 1954.
11. Costero, I., Chevez, A., Barroso-Moguel, R., and Pomerat, C. M.: Caracterizacion del Sistema Fibroblastico. VI. Morfologia de las celulas mesenquimatosas in vitro. Arch. Inst. Cardiol. de Mex., **25:** 125–170, 1955.
12. Murray, M. R.: Recent advances of tissue culture in cancer research. Experientia. **XV 8:** 289–294, 1959.
13. Weiss, P.: Interactions between cells. Rev. Mod. Physics, **31:** 449–454, 1959.

The Nature of Polymyositis and Related Muscular Diseases[1]

By DEREK DENNY-BROWN, M.D.[2]

IT IS INDEED an honor for a neurologist to be invited to give the Chouké Lecture and, at the same time, a challenge. The neurologist, with his interest in the locomotor system, has certainly a special point of view regarding such problems as polymyositis, and though he may seldom deal with primary allergic reactions, he is continually reminded that the tissues of nerve and muscle are subject to hypersensitivity. Dermatomyositis is a prominent example, and if I cannot contribute significantly to the nature of hypersensitivity in this disorder, I can try to define polymyositis more clearly. In this way perhaps I may hope to achieve something of the aim of your perceptive and generous Dr. Chouké.

The first difficulty in relation to any discussion of polymyositis is to define what is meant by "polymyositis." The most simple definition is that of the pathologist, namely an affection of muscle associated with a reaction in the supporting connective tissue. This associated response is not necessarily an inflammatory reaction in the strict sense, though it is customary to consider polymyositis in two general groups: 1) polymyositis due to parasitic or microbic invasion, and 2) polymyositis of unknown etiology. We may briefly note that trichinosis is the most usual parasitic invader of muscle encountered in this country, and that toxoplasmosis is very rare, though probably not as rare as formerly believed. Of the microbic types, that of Weil's disease is something of a curiosity, and I have not seen tuberculous myositis for many years now. Of the parasitic disorders trichinosis alone appears to set up a widespread cellular reaction in the connective tissue of muscles, apart from the destruction of such muscle fibers as are directly invaded.

I wish to discuss more particularly the types of polymyositis that are designated as those "of unknown etiology." Those have always presented a difficult problem to the clinician, for there appear to be many different varieties with all manner of variation of course and prognosis. We may distinguish at one end of the scale a relatively acute type of paralysis of proximal muscles of shoulders and thighs, with muscle tenderness and sometimes swelling and induration, associated with erythematous rash over the face, neck and chest, and sometimes the extremities, that we call acute *dermatomyositis*. It is most characteristically seen in children, and can run a relatively benign course of many weeks, with slow but eventually complete recovery. The onset is commonly associated with some recent infection, with or without the use of parenteral injections of foreign protein. It is therefore commonly regarded as a type of hypersensitivity reaction. It is remarkable however that recurrence after a long interval of time is virtually unknown, and that of the many kinds of myositis seen in adult life, I have yet to see a patient who had an attack of dermatomyositis in childhood.

This acute benign type of the disease also occurs in adults being then seen as acute swelling, pain and stiffness in the thighs, and commonly the calf muscles, developing at the height of an infection, commonly a streptococcal sore throat, and lasting 4 to 8 weeks or more before complete recovery. The cutaneous rash may or may not be present in the acute stage, as also in the childhood form. Since such an acute and benign form is often denied, an

[1] Hira S. Chouké Lecture III, College of Physicians of Philadelphia, 2 December, 1959.

[2] J. Jackson Putnam Professor of Neurology, Harvard Medical School, and Neurologist-in-Chief, Boston City Hospital, Boston 18, Massachusetts.

illustration of the edematous muscle seen in biopsy specimen, with sparse cellular infiltration around small venules is shown in Fig. 1A. The remnants of one necrotic muscle fiber are seen near a small venule that appears to be thrombosed. The patient, a woman aged 28 years, made a complete recovery in 9 weeks, and has remained well for 2 years.

Though dermatomyositis thus outlined is a relatively benign disease, it can lead to considerable contracture of muscles and to deformity if it is intense in the early stages. It is benign only in its self-limited course, and this is in fact subject to considerable qualification. Only 8 out of 26 children followed up by Wedgwood *et al* (1) had minor residual disability or complete recovery. The proportion of such recoveries is much less in series that include adult cases (2, 3). In the series reported by Wedgwood *et al*, the most acute onset was frequently associated with extensive, progressive and frequently fatal polymyositis. This is probably true of most hospitalized patients, for the benign type has been seldom seen in hospital by us, and is rarely subjected to biopsy verification. An acute onset had a better prognosis in Sheard's series (4).

Such an illness is only one aspect of a spectrum of myositic manifestations. At the other end of the scale is the condition called chronic polymyositis, where slowly progressive weakness and wasting of the proximal muscles of the lower limbs leads to difficulty in climbing stairs, and getting up from a chair. Gradually increasing difficulty in raising the arms points to added wasting and weakness of the shoulder muscles. In the course of weeks the hands and muscles below the knee become affected, the patient has difficulty in holding his head up, and may develop respiratory difficulty. The disorder may become arrested after weeks or months but tends to relapse, with great disability and a tendency to succumb to intercurrent infection. This condition is clearly different from dermatomyositis, in its course and in the rarity of associated skin rash.

Up to this point, then, we have in mind two very distinct conditions, and if we know little of their cause, we can at least see very different prognostic implications. Our difficulty begins with the dermal reaction, for an affection of muscles identical with that we have outlined for dermatomyositis may occur without any skin rash of any kind. For this reason many prefer the term *acute polymyositis, with or without dermal reaction*. Conversely the patient with what we have called chronic polymyositis may with late relapse present erythematous patches on face, chest, or extensor surfaces of limbs, though not of the florid type commonly seen in childhood dermatomyositis.

Not only has it been impossible to draw any sharp line of distinction between clinical states that are benign and those that are progressive and destructive, but all these clinical states can occur in association with disease of the connective tissues. Scleroderma in particular has this relationship which can be traced from the shiny indurated area of rash in otherwise uncomplicated dermatomyositis, to frank scleroderma with only incidental affection of muscles. Less frequently lupus erythermatosus and rheumatoid arthritis are associated. In general, the more chronic and more insidious the onset of polymyositis, the more frequently these related disorders appear. Chronicity of polymyositis and tendency to relapse should always lead to suspicion of more general disorder of this kind. The extreme situations of this type is represented by periarteritis nodosa, where the muscle lesions are only secondary to ischemic arterial lesions, and the nodular granulomas of sarcoid.

One can say in the Hibernian manner that the good prognosis of acute dermatomyositis is only valid in retrospect! One has no way of determining which case will relapse and which will not. Relapse occurs so frequently with some intercurrent fever, a streptococcal infection, a pneumonia, or in relation to sulfonamides or antibiotic used to combat these, that hypersensitivity is commonly held responsible. Steroid treatment is effective in proportion to the degree of involvement of connective tissue. But no satisfactory way has yet been found to determine the antigen.

An even more troublesome association has been that of carcinomatosis, reported in approximately 10 per cent of adult cases. Since this association is of special interest, we shall return to it later in this lecture.

In all these variants of polymyositis the amount of tenderness and induration of muscles, the distribution of affected muscles, and the usual impairment of muscle tendon reflexes can be similar. Chemical estimations of output of creatine have reflected only the bulk of muscle involved. Estimation of serum transaminase has shown raised levels corresponding to the acuteness and extent of recent destruction of muscle. The electromyogram shows the lessening of muscle action potentials corresponding with the extent of weakness, with abnormal irritability in recently damaged muscle fibers. None of these laboratory methods assists us in estimating the type and severity of the disease.

We therefore turn to *muscle biopsy* in search of the information we require. In acute dermatomyositis the biopsy sections of an affected muscle are most dramatic. There is intense cellular response in the connective tissue, with infiltrations, chiefly of histiocytes and lymphocytes (Fig. 1B). In the more acute cases polymorphonuclears may be present, and clumps of eosinophils can nearly always be found. Many of the larger muscle fibers are very swollen, but necrosis is infrequent and limited to part of a muscle fiber. The remaining muscle fibers are small and occasional fiber remnants are seen. There are always a great many small muscle fibers showing proliferation of large prominent muscle nuclei. Their cytoplasm is increased in relative amount and is frequently basophilic, a change that, in the absence of nuclear pyknosis, presages regeneration. After the first weeks many of the smaller fibers show newly developed myofibrils, and are clearly undergoing regeneration. After the first month the larger number of small fibers of normal appearance but with increased content of plump muscle nuclei indicates that regeneration is at an advanced stage. The cellular infiltrates have now become clumped in large masses, usually surrounding venules, and the cellular type is chiefly lymphocytic, with occasional eosinophils. Some fibroblastic proliferation of the connective tissue has usually occurred with associated collagenous change.

In summary then, the histology is that of a widespread but patchy reaction in the endomysial connective tissue. Necrosis of muscle fibers, the eosinophilic floccular swelling with invasion of their contents by histiocytes, affects only perhaps a portion of one fiber in many low power fields. When such necrosis occurs it is related closely to one of the cellular infiltrates.

In patients in whom the onset is more gradual over a period of months, in association with swelling and pain in joints as well as increasing stiffness and loss of bulk in muscles, with intermittent fever and fluctuating course, there is more intense fibrosis in the connective tissues. The muscle fibers become widely separated by collagen, many fibers of small diameter are seen (Fig. 1C). There are reactive changes in the muscle nuclei which become large, vesicular and more numerous. Necrosis is still a rare event (Fig. 1D) and is associated with active regenerative change. The change in muscular tissue is secondary to the changes in connective tissue. Though ultimately large numbers of muscle fibers are lost, their disappearance seems to be by attrition. When scleroderma has been the chief clinical manifestation, the connective tissue becomes heavily collagenous, or even calcified. The muscle fibers, though very small, show virtually no necrotic lesions.

If we have in mind this general histologic aspect of acute and chronic polymyositis and examine the muscles of case where the onset has been insidious, the course steadily progressive, without muscle tenderness and without dermal reactions, we find a different histological appearance. In such progressive types of uncomplicated myositis there is primarily one of three types of change: necrosis of muscle fibers, vacuolar nuclear degeneration, or granular (pigmentary degeneration). Cellu-

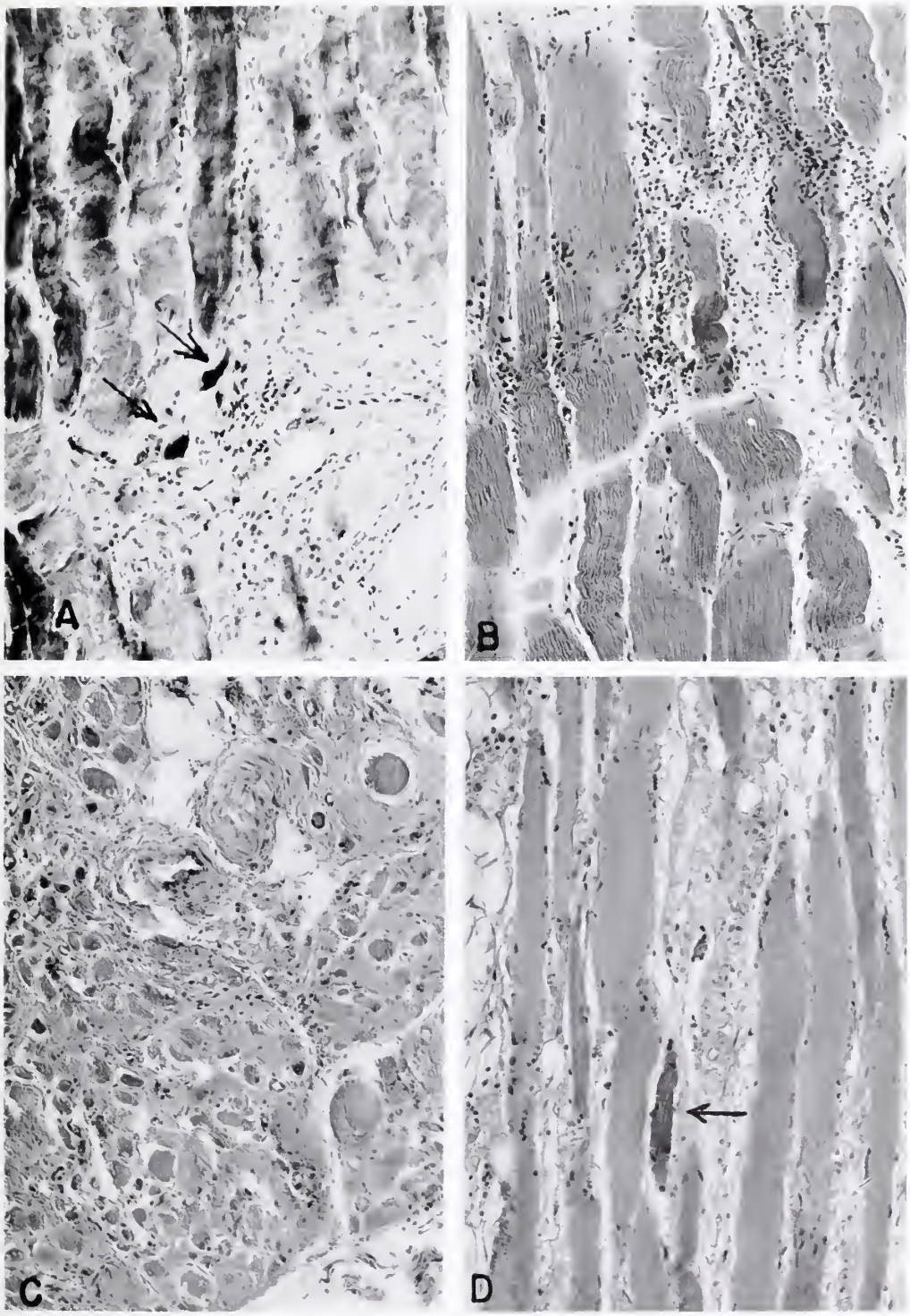


FIG. 1. A, Acute benign polymyositis with streptococcal infection. B, generalized "dermatomyositis," subacute, with severe weakness. C, sclerodermatous chronic polymyositis. D, longitudinal section of same muscle, arrow indicates one shrunken dark pseudonecrotic fiber. All hematoxylin-eosin.

lar reactions around damaged fibers may be present, but is limited to phagocytosis of each damaged fiber. Cellular collections may be found around an occasional venule, but are seldom prominent. The endomysial connective tissue is not primarily altered. Such necrotizing vacuolar and granular types of change have all been described by the earlier pathologists as aspects of degenerative muscle disease (5), but only in the most indiscriminate way. We have become convinced that they have more special significance in relation to polymyositis, and will discuss them separately.

PRIMARY MUSCULAR DEGENERATION

(Necrotizing Myopathy)

The most common type of such disease is a slowly progressive weakness and wasting of muscles, usually of quadriceps and the muscles of the pelvic girdle, and sometimes of the shoulders also. A characteristic example is that of a young woman aged 22 who has had difficulty in climbing stairs, or walking long distances, for two years. On examination weakness in flexion of either hip joint, extension of the knees, and of raising the arms above the shoulders was the only abnormality found. The deltoid muscles were slightly wasted, but all other muscle groups maintained good bulk. There was no family history of muscular weakness, no affection of lumbrosacral or of neck muscles, no history of skin rashes or of other illness. An injection of penicillin for a mild upper respiratory infection one year after the onset of weakness was associated with great increase in weakness in the following 3 weeks, with slow recovery to the initial status. Biopsy of deltoid muscle revealed in general normal muscle fibers and connective tissues, except that every here and there a muscle fiber could be seen either in recent necrosis, with phagocyte response, or in fragmentation with intense basophilia and doubtful regeneration (Figs. 2A, 2B). There were 3 or 4 such fibers in every low power microscopic field. In other places darkly basophilic small fibers or groups of muscle spindle cells appeared to be undergoing degeneration, for their nuclei were uniformly dark and pyknotic. The condition has become only very slightly worse in a further interval of over two years. Further biopsy has been refused because of the development of a keloid scar after the first.

A similar case was encountered in an 11-year old boy, and Walton and Adams (3), describe another (their case 3), a child aged $3\frac{1}{2}$ years, with continuing disability 3 years later. The clinical appearance of such disorder very closely resembles muscular dystrophy, and indeed an identical affection of both quadriceps muscles after middle age is usually called "late-life myopathy." Two cases reported by Nevin (6) are typical. We have seen the condition in 2 males aged 54 and 63 years respectively (Fig. 2C), and reported (7) the case of a woman aged 42 years, with the characteristic isolated necrotic fibers in biopsy section of quadriceps. Mumenthaler *et al* (8) have reported further cases. Walton (9) has described two cases but found only patchy disappearance of muscle fibers in a biopsy.

Names such as late-life myopathy, menopausal muscular dystrophy (10), late muscular dystrophy (8, 9) appear to the author to be inappropriate to a condition that can occur at any age, though more frequent in women after middle life. I shall therefore refer to it as "*necrotizing myopathy*." The prominence of necrotic muscle fibers sets it apart from muscular dystrophy. It is slowly progressive over a period of one to five years and then tends to become arrested, or to progress more slowly. The affected muscles do not show any interstitial reaction, even when a large proportion of the muscle fibers have disappeared. Cellular infiltration of the connective tissues is sparse, and usually absent in the early stages.

The condition of limited necrotizing myopathy, as thus described, is very distinctive. Yet, except for its slow course, it is clinically and pathologically indistinguishable from a type of generalized muscular degeneration beginning in the thigh muscles and spreading rapidly to other muscles in the course of 2 to 6 months. The amount of cellular change within necrotic fibers may then become im-

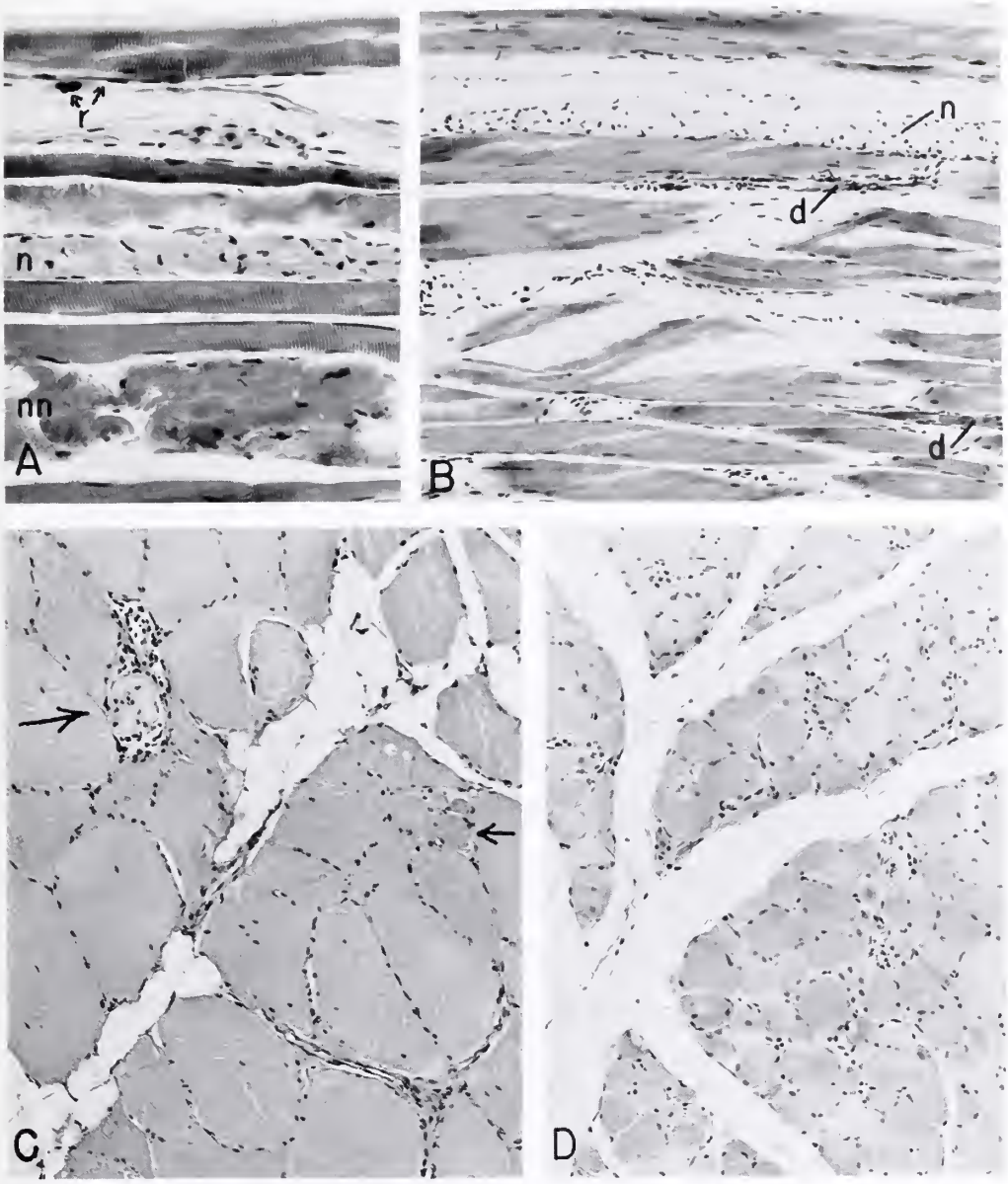


FIG. 2. "Necrotizing myopathy", to show at A a recently necrotic fiber, *nn*, a necrotic eosinophilic fiber containing histiocytes, *n*. At *r* are seen remnants of degenerate fibers. B, another section of the same muscle showing a necrotic fiber at *n*, and two intensely basophilic fiber remnants with pyknotic nuclei at *d*, *d*. Luxol fast blue. C section from calf muscle in another case, to show early and late fiber necrosis, in absence of other change, HE. D, to show large numbers of fibers in various stages of necrosis in a case of severe generalized necrotizing myopathy.

pressive, so that the condition is usually called chronic polymyositis (Fig. 2D). Cases 2, 13 and 14 of the series of polymyositis, two of them with secondary myoglobinuria, reported by Walton and Adams (3), are characteristic of this generalized severe and rapidly progressive type of this disorder. In general the muscular changes have the appearance of a toxic reaction with only mild and secondary changes in the connective tissues. Swelling and erythema of the face may be associated.

Some recent findings in an unusual me-

tabolic anomaly called "the McArdle syndrome" have thrown a new light on focal necrotizing disease of muscle. In 1951 McArdle (11) described a remarkable condition in a man aged 30 years. In this patient weakness, stiffness and aching pain in muscles had occurred after heavy exercise. Immediately after exercise the muscles remained shortened, firm and tender. These symptoms disappeared in minutes if the exercise had been mild, but persisted for hours or days after strenuous exercise. Exercise failed to cause the blood lactate or blood pyruvate to rise as in a normal subject. The muscles appeared to be unable to utilize glycogen. A muscle biopsy was not performed.

This condition had not again been reported until our colleague Dr. Schmid encountered a further case in 1957, described in detail recently by Schmid and Mahler (12). This second case, a man aged 52, who has 8 siblings without muscular disease, has suffered from muscle cramps, stiffness, pain and weakness following any severe exertion since the age of 18. In 1948 he was reported by Kreutzer *et al* (13) as a case of myoglobinuria, produced by exertion. A fall in blood lactic acid during exercise was noted. By 1957 this patient was suffering from persistent weakness and atrophy of proximal muscles, especially quadriceps and biceps brachii. In 1958 Schmid and Mahler (14) found that there was no rise of blood lactate with muscular exercise, and were able to show that the defect was due to absence of phosphorylase in the muscles of this patient. The synthesis of glucose in the muscle by the VDPG route was active. The muscle could utilize glucose-6-phosphate, but had a five-fold increase in glycogen content. In histologic section granular material, positive by PAS and Best's stain, distended the sarcolemmal membrane in large blebs (Fig. 3A). Muscle fibers that had the sarcolemma lifted in this way from their entire circumference were undergoing necrosis. As a result of repeated loss of fibers the quadriceps muscle showed areas of fat replacement. Glucose and insulin, or better glucagon, resulted in relief from cramps or muscle damage.

This year a further case has been reported in abstract by Pearson and Rimer (15) and by Mommaerts *et al* (16) in a young man of 19, closely resembling McArdle's first patient. Phosphorylase was also lacking in the muscles of this patient but no significant destruction of muscle had occurred. Mahler has now found five other cases, 2 in the same family (12).

The significance of the McArdle syndrome for our present discussion is two-fold. The finding of absence of phosphorylase has now demonstrated a metabolic mechanism which can cause necrosis of isolated muscle fibers. In this case the disorder is present throughout life, and the attacks are episodic in relation to exercise. The muscles chiefly affected are the large proximal muscles, and the ultimate atrophy closely resembles that of the more chronic types of polymyositis. It is now likely that patients suffering from exertional myoglobinuria are indeed suffering from the McArdle syndrome. As Korein and his associates (17) have recently pointed out, this type of myoglobinuria (Group I) in all reported cases began between the ages of 12 and 55 (most between 15 and 23), ran a very slow course, were seldom febrile and seldom fatal. The other type of myoglobinuria ("toxic myoglobinuria") occurs at all ages, is more commonly precipitated by antecedent infection, is associated with fever and is fatal after fewer attacks in a shorter period of time.

The second fact that appears very significant for our present discussion emerges from the finding that in Schmid's patient myoglobinuria now seldom occurs. Myoglobinuria is in him an index of the intensity and extent of muscle damage. Had we not the observations of Kreutzer on this patient, we would not now suspect his previous massive myoglobinuric attacks. This immediately draws attention to the group of cases we have called necrotizing myopathy. In such cases the affected muscles are the same, and aching on exertion has been a symptom reported in many cases, including that reported by me in 1939. Only further investigation of such cases can decide whether they suffer from a similar

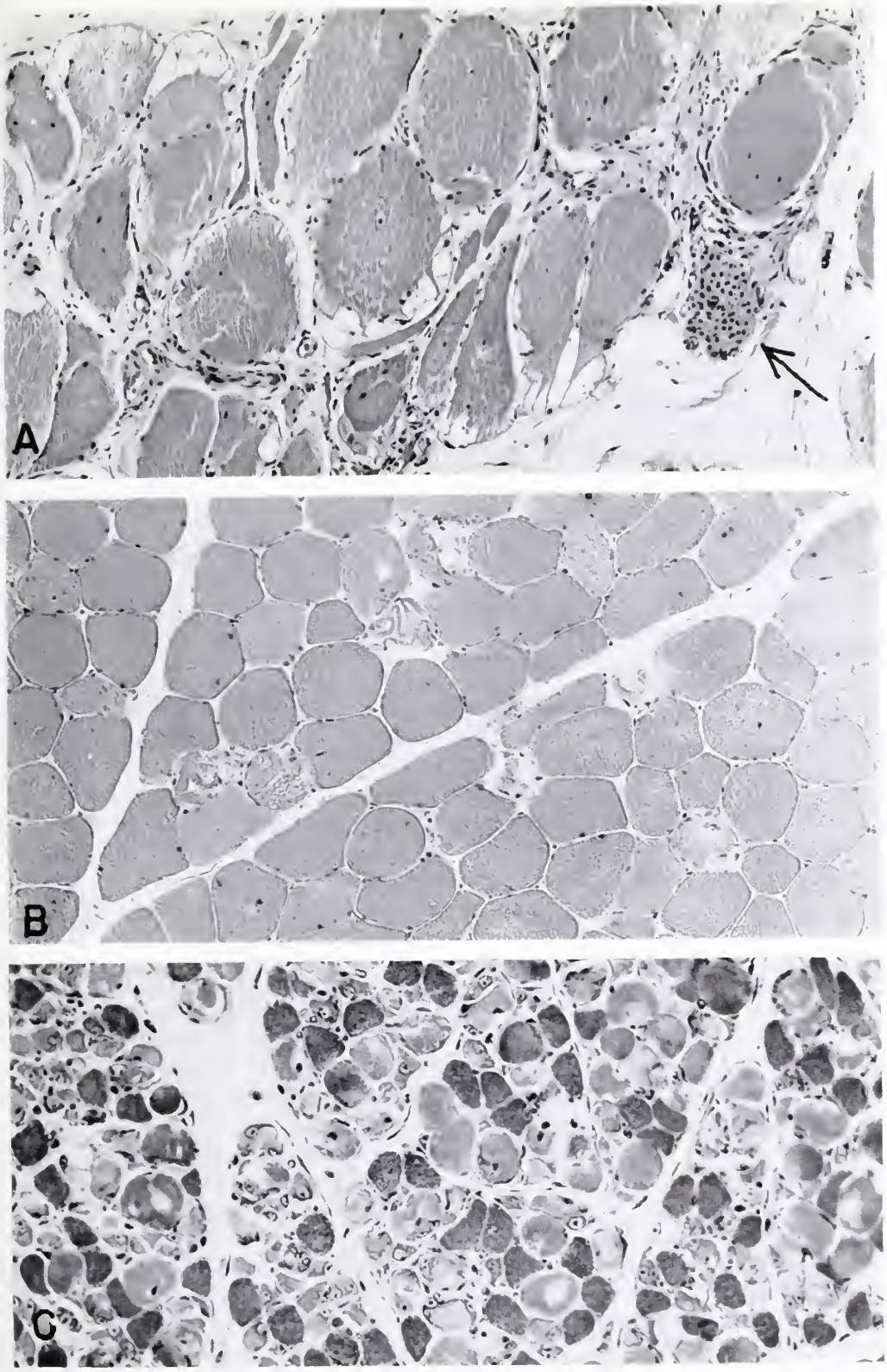


FIG. 3. A, section of calf muscle in McArdle syndrome (from Schmid and Mahler's case). Arrow indicates necrotic fiber. Fiber remnants are seen at lower border of figure. Eosin-meth. blue. B, from fatal case of "spontaneous myoglobinuria" to show early selective necrosis. C, from recovery stage (10th day) in myoglobinuria of childhood (courtesy of Dr. John Craig).

defect. Their pathology certainly suggests a similar, if not identical metabolic fault.

Toxic myoglobinuria (Group II of Korein *et al*) is also associated with necrosis of muscle fibers. It is of interest that in mild attacks the necrosis is very selective, involving only isolated fibers in many muscles (Fig. 3B). In recovery from an attack an astonishing degree of regeneration of the damaged fibers can occur (Fig. 3C) accounting from the absence of ultimate atrophy in this type of disease. Such regeneration is absent in the few cases of exertional myoglobinuria I have seen. In either type of myoglobinuria a severe attack can lead to necrosis of large areas of muscle with consequent severe renal damage. Cases of generalized "necrotizing myopathy," where muscle necrosis has been a widespread association, (subacute "polymyositis") have been too seldom analysed to enable their relationship to the two main types of myoglobinuria to be established with certainty. "Muscular dystrophy" with isolated attacks of myoglobinuria appear to represent a chronic form of this general group of disorders, of such kind that the muscles become only gradually depopulated of muscle fibers. In three such cases reviewed by Hed (20), as also Schmid and Mahler's case reviewed by us, the calf muscles were significantly enlarged. In the latter case we found that the enlargement was a true hypertrophy, also in 3 cases of what we would call necrotizing myopathy. We doubt the occurrence of pseudohypertrophy reported by Walton and Adams (3) in chronic polymyositis and would not be convinced that true genetically determined muscular dystrophy is associated with necrotizing myopathy.

The toxic agent that provokes attacks of necrosis in non-exertional myopathy of this type is unknown. The onset in some patients has been associated with alcoholic excess (18, 19). Low carbohydrate diet is known to facilitate the appearance of exertional myoglobinuria (20) and may be the crucial factor in relation to alcoholism. The acute necrotizing myopathy that may occur with hyperthyroidism can also be associated with myoglobinuria (20) which can also be seen with the infectious necrotizing myopathy of Bornholm disease. All these conditions should be sharply differentiated from the myoglobinuria with focal necrosis caused by ischemia, as in pretibial syndrome, crush injury and probably also the postural pressure ischemia associated with carbon monoxide poisoning.

The generalized form of necrotizing myopathy has in the past been described as "myositis" or "polymyositis." Dermal reaction other than erythema has not been reported. The first muscles to be affected are usually the proximal muscles in the lower limbs, but with increased severity the proximal muscles of the upper limb, of the neck and of swallowing are also affected, closely resembling other types of polymyositis. The absence of interstitial cellular infiltrations was noted in six of twenty-five cases of "polymyositis" and in three cases of "classic dermatomyositis" by Eaton (21). It was not stated how extensive such collections were in the remainder. We have found small cellular infiltrations in places in many cases of necrotizing myopathy, but in no case could it be said that there was an endomysial reaction. The extent of necrosis is also a relative one. It should also be emphasized that only when necrosis is the primary change, or alone accounts for weakness is the term necrotizing myopathy justified. It is necessary to exclude trichinosis though this does not in fact cause necrosis of more than small lengths of muscle fiber. Since all transitions are found between generalized and limited forms of necrotizing myopathy, we classify them together in the same group.

PROGRESSIVE VACUOLAR POLYMYOSITIS

Since polymyositis was first described by Wagner in 1863 vacuolation of muscle fibers has been noted from time to time. Multiple small vacuoles are commonly seen in the muscle fiber that is swollen by acute necrosis, from any cause. In one of the early accounts Unverricht (22) mentioned vacuolation as a prominent feature. The vacuoles were large and contained muscle nuclei. Unverricht also

noted the absence of evidence of regeneration of muscle fibers in this case, and the correlation of this feature with progressive loss of structure and function. The significance of this observation appears to have been lost, partly because vacuolation of muscle fibers is seen as a non-specific change in other conditions such as ischemia, and in metabolic diseases such as periodic paralysis. Yet, as we noted in our account of polymyositis in our book on muscle disease (23) there is a type of chronic progressive polymyositis where vacuolation of muscle fibers is unique. The material reported there was from a boy of 13 years who died after a progressive weakness of all limbs of insidious onset and 6 months' duration. There was a patchy, scaling psoriatic facial rash. I have since seen two other cases, in a woman of 33 years and a man 35 years of age. In such cases the muscle fibers at the edge of each fasciculus are most affected, giving a distinctive appearance on cross-section of the muscle. The muscle fibers that are least affected show a series of large vacuoles containing either large pale muscle nuclei in groups of 2 or 3, or shrunken pyknotic nuclei and nuclear remnants (Figs. 4A & B). The segments of the fiber between the vacuoles present a relatively normal appearance. In places in the endomysium there are occasional collections of lymphocytes around a small venule, but the connective tissue and blood vessels are not otherwise altered. There is no necrosis of muscle fibers, but only a progressive vacuolar loss of their contents, leading to small tubes with pyknotic nuclear residue (Figs. 4C, 4D). The course of the disease extends over some 8 to 18 months with fatal outcome. No associated pathology was found in one autopsy case studied by me. Coërs (24) describes a typical case in a man aged 40 with some improvement following treatment by ACTH. The ultimate course is not mentioned. There was associated fever and raised sedimentation rate. In another case recently reported by Pearson (25), minimal vacuolar change of the same kind was reported. A positive LE preparation was eventually obtained after many negative stains. The vacuolar change has not been specifically commented on in other cases of lupus erythematosus where only occasional "inflammatory" nodules have been reported.

Vacuolar myositis therefore stands apart from the types of change we have called acute and chronic polymyositis, and from necrotizing myopathy, by reason of its unusual type of damage to the muscle cell, and its steadily progressive character. I might also add that it tends to affect *all* muscles in the limbs, not just the proximal muscles. In our limited experience of it the prognosis has been very poor. We have observed it in muscle biopsy in a young woman, whose first weakness was of myasthenic type, and who subsequently developed a severe generalized weakness of proximal muscles following penicillin sensitization and transient rash. She improved considerably with treatment by ACTH and cortisone, only to develop breast carcinoma a year later. At that time she was still greatly disabled by her polymyositis. In our one autopsy case, there was no associated carcinoma.

CARCINOMATOUS MYOPATHY

The association between malignant disease and dermatomyositis received little attention until the reports of Bezecny (26) in 1935 and O'Leary and Waisman (2) in 1940. Since then many cases have been reported, recently reviewed by Walton and Adams (3) and by Williams (27). The incidence of carcinoma in relation to any group of cases of polymyositis has varied between 5 and 17.7 per cent. The related carcinoma has been often pulmonary in origin, but as frequently in breast, stomach and ovary. A significant number of cases has been reported in a great variety of types of carcinoma, together with leukemia and thymoma. In a number of cases with bronchogenic carcinoma and in some with breast carcinoma there has been an associated myasthenic syndrome. The onset of the polymyositis may precede, accompany or follow removal of the carcinoma. It may recover while the carcinoma continues, or worsen

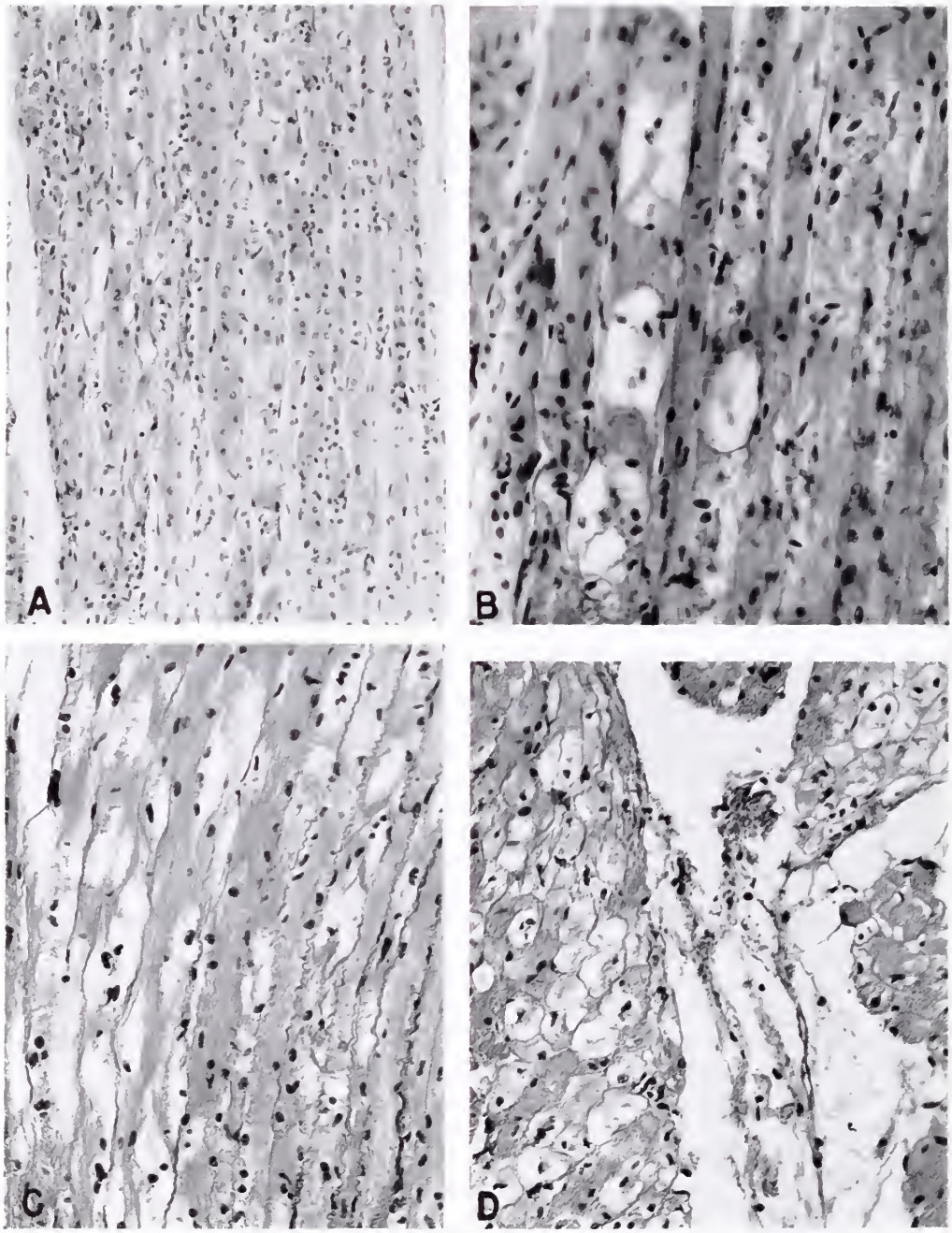


FIG. 4. Vacuolar myopathy. A, from severely affected psoas muscle, H.E. B, higher magnification of same muscle, iron hematoxylin. C, D, from another case. H.E.

after a pulmonary carcinoma is removed *in toto*. In relatively few instances removal of the carcinoma has resulted in recovery from polymyositis.

We are therefore unable to make any useful generalization as to the nature of this relationship. All that can be said at this time is that in many such cases the polymyositis has had the histological characteristics and general prognosis of dermatomyositis including a rash

on face and neck in some cases. If the polymyositis is evidence that the patient has developed a hypersensitivity reaction to his own tumor tissue, as Brain and Henson (28) have suggested, the response has borne remarkably little relation to the presence of the antigen.

Drs. Marin and McHenry in our laboratory have recently found a remarkable phenomenon in relation to the cachexia of patients suffering from ovarian carcinoma, in less degree with other types of carcinoma (breast, rectum, lung), and in some degree with all cachexia, that is more directly related to the presence and course of the growth. This condition is a pigmentary degeneration of the contents of the muscle cell, resulting in its transformation into granular lipofucsin, and eventual dissolution. The muscle nuclei congregate in degenerate clumps. This change, called "pigmentary muscular atrophy" by the older authors (5), is found in a few muscle fibers in many chronic cachectic states. It is certainly a metabolic change, the nature of which remains to be determined. In one case of ovarian carcinoma and one of rectal carcinoma this change was generalized in the proximal muscles, so that in large areas little remained of the muscle fibers (Fig. 5A). In other areas the fibers had ruptured into large fragments. The resulting nuclear proliferation and aggregations were intense, yet the connective tissues, blood vessels, and nerves were unaffected. In the most severely affected areas many of the largest fibers had broken into segments, with occasional phagocytic invasion by histiocytes. Such necrosis was minimal in degree compared with what we have called necrotizing myopathy, where it is seen in every affected fiber. There was no evidence of regenerative activity, not even of basophilia. In the least affected muscles such nuclear degeneration was alone present (Fig. 5B), without necrosis. There was no associated cutaneous reaction. Such cases demonstrate that the muscular reaction to carcinomatosis is by no means a uniform entity, and includes at least one type of metabolic reaction, the "granular pigmentary muscle degeneration" of cachexia. The histology of the case No. 6 reported by Coërs (24) also has this appearance in association with mammary carcinoma. The lack of specificity of this progressive granular degeneration with nuclear clumping was emphasized for us by the case of a woman aged 49 suffering from mild hyperthyroidism, with no previous illness except pneumonia at the age of 9, who developed painful swelling and weakness of muscles in both lower limbs. The weakness progressed steadily, leading to complete paralysis of both lower limbs, and involved the upper limbs and trunk musculature after 9 months. Death from bronchopneumonia occurred in the 11th month of illness. There was no pigmentation of urine. All muscles showed some degree of muscle fiber degeneration, with intense nuclear clumping (Fig. 5C) and granular change, and fragmentation. Similar clumping is also a feature of a late stage of atrophy in denervated muscle (29) but is not then associated with granular or pigmentary changes. There was no regeneration, and but rare necrosis, and lymphocytic infiltrations were perivascular and discrete. There was no angiitis. No carcinoma was found.

The case discussed by McCoombs and MacMahon (30) where discrete circumscribed areas of yellowish-gray patches of muscular degeneration occurred in a patient with bronchogenic carcinoma presented an unusual type of lesion. The patchy complete necrosis of muscle was associated with angiitis of muscle and other organs, and it is doubtful if the muscle lesions were primary. Yet a dermal lesion on exposed areas was present. Skin reactions may certainly occur alone in relation to carcinoma (31), and the link to muscle lesions in this case appears to have been periarteritis, a hypersensitivity reaction. Walton and Adams (3) in noting the relative absence of inflammatory reaction in their cases of polymyositis associated with carcinoma question a possible metabolic factor other than a hypersensitivity reaction. They were however not impressed by any other difference between cases with malignant disease and other types of polymyositis. The differ-

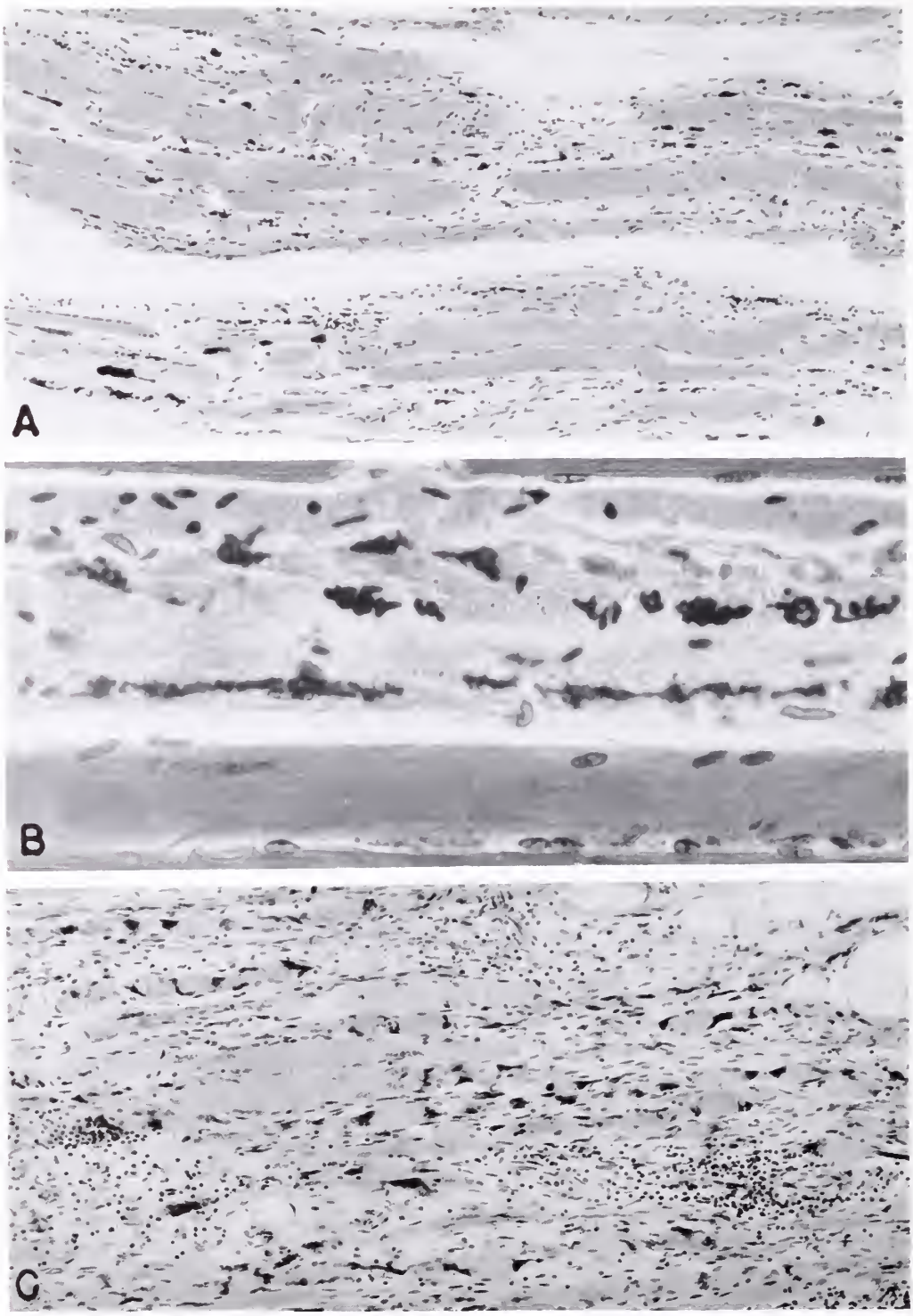


FIG. 5. "Granular degeneration." A, in muscle of abdominal wall of patient with ovarian carcinoma. H.E. B, higher magnification of the same muscle, to show granules and clumping of nuclei in affected fibers, Masson trichrome. C, from quadriceps muscle of case of severe generalized myopathy with mild hyperthyroidism. Iron Hem. and Van Gieson.

TABLE I

1. POLYMYOSITIS < ACUTE / CHRONIC (Dermotomyositis)
with or without dermal lesion

2. NECROTIZING MYOPATHY
a. ACUTE GENERALIZED
with myoglobinuria
b. CHRONIC INTERMITTENT
with intermittent myoglobinuria
c. CHRONIC LIMITED (Quadriceps)
slowly progressive

3. VACUOLAR MYOPATHY
chronic progressive

4. GRANULAR (Pigmentary) DEGENERATION
progressive, with or without cachexia

ences we have outlined here lead to a different conclusion, but much detailed analysis of further cases is clearly needed before absolute generalizations can be made.

DISCUSSION

Our material has been derived from sixty cases of different types of myositis with biopsy or autopsy verification seen in the last twenty years. After discarding eleven cases because of insufficient biopsy material, or unsatisfactory sections, over half (28 of 49) presented primary connective tissue changes (acute and chronic polymyositis, scleroderma, and two cases each of periarteritis and sarcoid). There is much to indicate that a hypersensitivity response is the primary factor in this group. A fifth of our classified cases (10 cases) showed primary necrotic changes in muscle, and a fifth (11 cases) showed granular types of degeneration, except for three cases of the peculiar condition we have called vacuolar myopathy. Though all these four types of change (Table I) are recognizable in descriptions of "Dermatomyositis" and "Polymyositis" by others in the past, the term "Polymyositis" is used by us only for such cases where there is a florid reaction in the connective tissue, with minimal or clearly secondary degeneration in muscle fibers.

Primary necrosis of isolated muscle fibers is a striking lesion, and none the less unique when it is widespread in the absence of vascular disease. For this we prefer the term "necrotizing myopathy." Though most usually found in relatively limited and chronic affections of proximal muscles in the lower limbs, it can at times become a progressive generalized disease. The recent identification of a metabolic defect in glycolysis in one type of such case, associated with necrosis of muscle fibers and myoglobinuria following severe exertion indicates one mechanism for such a condition. It appears likely that other types not related to exertion, and the corresponding spontaneous myoglobinuria will have some similar metabolic disorder. The very discrete lesions of this type of necrotizing myopathy indicate some abnormality arising within the isolated muscle cells, and therefore unlikely to be related to protein hypersensitivity. Dermal reactions are not usually associated.

The third type of disorder, that might be called vacuolar myopathy, indicates some particular type of degeneration of the perinuclear cytoplasm of the muscle cell, and is therefore probably also metabolic in origin. It is rarely encountered, and offers less opportunity for study. A dermal reaction may occur.

The last type of myopathy is evidenced by degeneration of clumped nuclei, with granular disintegration of the contents of the muscle cell. Its common association with cachectic states, and with carcinoma with or without cachexia, leading sometimes to widespread "polymyositic" degeneration in a few months, also suggests a specific metabolic type of failure. There is a breakdown in the protein contents of the muscle fiber. A hypersensitivity of the skin may be associated. In other cases dermatomyositis of the type we have called acute polymyositis has occurred in indirect relation to carcinoma, in a manner that suggests chance coincidence.

Whereas regeneration of muscle fibers is usual in acute and even chronic varieties of Type I polymyositis and in acute varieties of Type II, such regeneration is completely absent in those conditions we have classed as Types III and IV, as well as the more chronic variations of Type II. This is in line with the lack of recovery of the wasted muscles in the

corresponding clinical syndromes. Myoglobinuria can be expected only with Type II, being secondary to widespread necrosis of the muscle cells.

Much of the difficulty in assessing polymyositis in the past has arisen from inability to find criteria to distinguish between cases with differing prognosis and probable causation. It is hoped that with more attention to the types of disintegration of the muscle cell that we have outlined, a more satisfactory understanding of this heterogeneous group of diseases may be gained. Muscle biopsy is a simple and direct procedure. The chief objective of histological assessment of muscle biopsy should be to determine the type of primary damage to the muscle cell. Too frequently the piece of muscle is too small or too distorted for accurate diagnosis. It is necessary to caution however that it is essentially a sampling procedure, and that it is necessary to select a partially involved muscle to see the type of damage to best advantage. Second, in all types of muscular damage necrosis of occasional fibers may be seen, with minor vacuolation. Lastly, that ischemic lesions relating to primary angiitis may simulate widespread necrotizing myopathy yet belong essentially to the diseases of supporting tissues characteristic of Type I.

With these criteria in mind, the search for the antigens that are surely active in Type I polymyositis may be more successful than in the past. Better definition of the other types of primary degeneration of the muscle cell will offer valuable clues to the nature of metabolic defects.

REFERENCES

1. Wedgwood, R. J. P., Cook, C., and Cohen, J.: Dermatomyositis: Report of twenty-six cases in children with a discussion of endocrine therapy in thirteen, Pediatrics **12:** 447, 1953.
2. O'Leary, P. A., and Waisman, M.: Dermatomyositis: A study of forty cases. Arch. Derm. Syph., N.Y. **41:** 1001, 1940.
3. Walton, J. N., and Adams, R. D.: *Polymyositis*, Livingstone, Edinburgh, and Williams and Wilkins, Baltimore, 1958.
4. Sheard, C.: Dermatomyositis. Arch. Int. Med. **88:** 640, 1951.
5. Durante, G.: Anatomie pathologique des muscles, pp. 1–477, in *Manuel d'Histologie Pathologique* ed. by Cornil and Ranvier, Félix Alcan, Paris, 1902.
6. Nevin, S.: Two cases of muscular degeneration occurring in late adult life. Quart. J. Med. **5:** 51, 1936.
7. Denny Brown, D.: Myopathic weakness of quadriceps. Proc. Roy. Soc. Med. **32:** 867, 1939.
8. Mumenthaler, M., Bosch, T., Katzenstein, E., and Lehner, F.: Ueber den isolierten Befall des M. Quadriceps femoris bei der Dystrophia Musculorum Progressiva. Confin. Neurol. **18:** 416, 1958.
9. Walton, J. N.: Two cases of Myopathy limited to quadriceps. J. Neurol. Neurosurg. Psychiat. **19:** 106, 1956.
10. Shy, G. M., and McEachern, D.: The clinical features and response to cortisone of menopausal muscular dystrophy. J. Neurol. Psychiat. **14:** 101, 1951.
11. McArdle, B.: Myopathy due to a defect in muscle glycogen breakdown. Clin. Sci. **10:** 13, 1951.
12. Schmid, R., and Mahler, R.: Chronic progressive myopathy with myoglobinuria: Demonstration of a glycogenolytic defect in the muscle. J. Clin. Invest. **38:** 2044, 1959.
13. Kreutzer, F. L., Strait, L., and Kerr, W. J.: Spontaneous myohemoglobinuria in man. Arch. Int. Med. **81:** 249, 1958.
14. Schmid, R., and Mahler, R.: Syndrome of muscular dystrophy with myoglobinuria: Demonstration of a glycogenolytic defect in muscle. J. Clin. Clin. Invest. **38:** 1040, 1959.
15. Pearson, C. M., and Rimer, D. G.: Evidence for direct utilization of fructose in working muscle. Proc. Soc. Exp. Biol. Med. **100:** 671, 1959.
16. Mommaerts, W. F. H. M., Illingworth, B., Pearson, C. M., Guillory, R. J., and Seraydarian, K.: A functional disorder of muscle associated with the absence of phosphorylase. Proc. Nat. Acad. Sci. **45:** 791, 1959.
17. Korein, J., Coddon, D. R., and Mowrey, F. H.: The clinical syndrome of paroxysmal paralytic myoglobinuria. Neurology **9:** 767, 1959.
18. Biörck, G.: On myoglobin and its occurrence in man. Acta med. Scand. Suppl. 226, 1949.
19. Elek, S. D., and Anderson, H. F.: Paroxysmal paralytic myoglobinuria. Brit. Med. J. **2:** 533, 1953.
20. Hed, R.: Myoglobinuria in man, with special reference to a familial form. Acta med. Scand. Suppl. 303, 1955.
21. Eaton, L.: The perspective of neurology in regard to polymyositis. Neurology **4:** 245, 1954.
22. Unverricht, H.: Dermatomyositis acuta. Dtsch. med. Wschr. **17:** 41, 1891.

23. Adams, R. D., Denny-Brown, D., and Pearson, C. M.: *Diseases of Muscle, A Study in Pathology.* Hoeber, New York 1953.

24. Coërs, C.: Sur quelques types cliniques et histologiques de polymyosites. Rev. Belg. Path. Med. Exp. **25:** 369, 1956.

25. Pearson, C. M., and Yamazaki, J. N.: Vacuolar myopathy in systemic lupus erythematosus. Amer. J. Clin. Path. **29:** 455, 1958.

26. Bezecny, R.: Dermatomyositis. Arch. Derm. Syph. Wien. **171:** 242, 1935.

27. Williams, R. C.: Dermatomyositis and malignancy: A review of the literature. Ann. Int. Med. **50:** 1174, 1959.

28. Brain, R., and Henson, R. A.: Neurological syndromes associated with carcinoma: The carcinomatous neuromyopathies. Lancet **2:** 971, 1958.

29. Denny-Brown, D.: Experimental studies pertaining to hypertrophy, regeneration and degeneration. Proc. Assn. Res. Nerv. Ment. Dis., Vol. 38 (in press).

30. McCombs, R. P., and MacMahon, H. E.: Dermatomyositis associated with metastasizing bronchogenic carcinoma. Med. Clin. N. America, **31:** 1148, 1947.

31. Becher, S. W., Kahn, D., and Rothman, S.: Cutaneous manifestations of internal malignant tumor. Arch. Dermat. Syph. **45:** 1069, 1942.

The Use of Enzymes for Therapy[1]

By WILLIAM S. TILLETT, M.D.[2]

IN ADDRESSING remarks to a subject dealing with enzymes in therapy, it is not inappropriate, at the beginning, to comment briefly on some broad aspects of the subject of enzymes. Such an effort, if done adequately, would require a comprehensiveness of biochemistry and biology far beyond my capacity or purpose. However, a few general remarks are in order, by way of calling attention to the potential possibilities of this form of therapy. I do so by indicating, first, that it is a source of therapeutic reagents as yet scarcely tapped, and, secondly, it constitutes a unique form of treatment that may be dramatically effective but does not conform to the pharmacological principles on which the actions of most drugs are based.

It is correct, I believe, to assert that enzymes constitute the most important units in living matter. Every act of anabolism, metabolism, and catabolism involves them by the score. At the beginning of any type of cellular life, the initiating events that culminate in the living organism, be it unicellular or multicellular, is presided over by enzymatic catalysis. The duration of the period of viability is conditioned by the relentless continuation of multiple enzymatic metabolic processes supplying energy and tissue replacement. Finally when the end of life is reached, the degradation of the former living matter is effected by enzymatic processes.

The extent to which they hasten biochemical reactions is their most remarkable achievement. In their presence and influenced by them, changes in organic and inorganic matter occur in seconds, minutes, hours or a few days. Without their catalytic influence, change in matter, as we understand it, is so retarded that it must be measured in geological eras.

I make this brief eulogy of enzymes in an attempt to give to the substance of my remarks an orientation that emphasizes the potential scope of the topic of the utilization of enzymes for therapeutic purposes. The optimism with which I view the future development of the topic will become apparent, at least on theoretical grounds. The difficulties to be encountered will also be viewed realistically.

One large group of diseases is identified at present as metabolic disorders. Their practical therapy of today, when effective, requires the use of reagents, which directly or indirectly, influence metabolic enzymatic actions either by replacing an insufficient one, rendered imperfectly operative by disease, or by inhibiting excessive metabolic actions. Without going into details, brief mention in this connection might be made of insulin, or specific vitamins for specific diseases referable to their insufficient availability, and some of the products of endocrine glands. Except for those engaged in technical biochemical research in this field, I suspect that the average clinician is not clearly aware that the fundamental changes brought about by the specific therapy of metabolic disorders belong in the particular category that I refer to as enzymatic therapy. How startling the favorable effects can be, illustrating at the practical clinical level, the rapidity with which enzymatic catalysis of biological behaviour restores the situation to normal, when the proper conditions are fulfilled.

In addition to metabolism, there are additional areas of powerful enzymatic activity, on the one hand anabolic processes through which the biosynthesis of tissues is continually being accomplished and catabolism through

[1] Nathan Lewis Hatfield Lecture XLIV, College of Physicians of Philadelphia, 6 January 1960.

[2] Professor of Medicine (Emeritus), New York University College of Medicine, 550 First Avenue, New York 16, New York.

which the debris of tissues is continually being removed. For their use in the reconstruction of tissues, the possibilities of restoration through enzymatic processes has not been touched, in spite of the fact that defects in patient recovery that are reflected in permanent damage to organs even after the disease processes have become inactive, constitute a major therapeutic problem. For example, it is well known that, in the experimental animal, 80–90% of the normal liver may be extirpated and in a relatively short time this organ will return to its normal size with all its intricate functioning parts. However, if 80–90% of the liver is destroyed by disease, such as cirrhosis, the organ is helpless to regain substantial amounts of its normal structure. Under these conditions of disease nature has only recourse to repair through the deposition of fibrous tissue. If you will leniently view the disease situation from the point of view that I depict, the essential difficulty in cirrhosis of the liver lies in the absence or depression of the anabolic enzymes, which in the normal animal following surgical excision quickly restore normal liver tissues.

The third group of enzymes, the catabolic ones, break down tissues. There have been a few of these employed in practical therapy, including the two of streptococcal origin—streptokinase and streptodornase—which my associates and I and others have studied and reported extensively upon. I should like to describe certain features of their actions and mode of actions, and to stress the fact that such success as has attended their use has been derived from efforts to identify certain principles with which compliance is necessary if the therapy can be successful. This matter of the principles involved holds true either with these two particular enzymes or any others that in the future may be applied as a method of obliterating diseased states.

In the broad field of enzymological actions, including those slanted toward therapy, there are qualitative elements that require identification and quantitative elements that require measurement. When enzymatic actions are measured in vitro—in test tubes—the quantities of the required materials may be continuously and accurately controlled, such factors as temperature, hydrogen ion concentration, electrolyte content are maintained in an orderly fashion, and the high purity of each increment eliminates confusing side reactions. However, when attempting to determine enzymatic actions—in vivo—within the body, the quantitative factors are difficult to maintain in constant relationships, and the many side effects and other interactions associated with the total body content of innumerable biological actions occurring simultaneously, may introduce many difficulties both in actual results as well as their correct interpretation. However, since the word therapy deals with happenings in vivo, these unavoidable difficulties must be recognized and the plan of therapy adjusted to their existence. In order to illustrate in a practical way, the qualitative and quantitative factors that must be taken into account, I would like to review briefly the directions of study which my associates and I have taken in investigating the practical therapeutic effectiveness of the two enzymes of streptococcal origin—streptokinase and streptodornase (1).

I would first like to call attention to certain special biological aspects of the streptococcal enzymatic phenomena. The two enzymes, SK and SD, that hemolytic streptococci have presented to us for study are dissimilar in every respect. Both their production by the growing microorganisms and mode of action are entirely independent of each other. They may be produced simultaneously by the same strain, or produced singly by other individual strains. However, they do have one common denominator that is of considerable interest and deserves attention. Fibrin, which the SK system attacks, and desoxyribonucleo-protein, which SD attacks, both belong to the same group of chemical substances which are defined as fibrous, insoluble proteins, as contrasted with globular soluble proteins, such as albumin or globulins and many others. Although the two fibrous proteins just men-

tioned are entirely different in chemical structure, they have identical physical properties consisting of coarseness, stringiness, and stickiness. Consequently, when either or both of them appear as constituents of pathological processes they pose a particularly difficult problem for the body to eradicate through its own native processes of recovery.

Fibrin as such does not exist in tissues under normal conditions. When transformed from its precursor fibrinogen, it emerges with great frequency as a result of trauma or disease. Because the prime function of fibrin is to arrest hemorrhage by creating a mechanical barrier, nature has endowed this barrier with a tenacious insoluble quality that is not subject to rapid disintegration.

Similarly DNA-protein is thick, viscous, and stringy, properties which account for the tenacious quality of purulent exudates. When such exudates occur in closed areas of the body not amenable to open drainage, their eradication by the efforts of the body's mechanisms is slow and often unsatisfactory with resultant deep-seated scar formation.

At this point it is interesting to note that of all the proteins that make up the tissues of the body, only fibrin, DNA-protein, and connective tissue proteins such as collagen, reticulin, and elastin belong to the group of the fibrous insoluble type.

It is intriguing, therefore, in a speculative fashion, to ponder the question of how does it come about that one single group of bacteria namely beta hemolytic streptococci, in their emergence through ages of evolution have acquired these two separate and independent enzyme systems that attack two protein substrates that have the special physical properties just described. As a generalization, it may be stated that the biological properties of any viable cell serve one of three purposes, namely nutrition, reproduction, or self protection. Which of these three purposes do SK and SD fulfill for hemolytic streptococci? It would take me too far afield to extend this kind of speculation. However, any attempt to go to the grass roots of the bases of bacterial pathogenicity inevitably leads to speculations such as I have just mentioned. With respect to hemolytic streptococci the problems referable to their extracellular products are particularly provocative, because of the special multiple mechanisms by which this bacterial species incite so many different clinical entities. Before completely leaving this area of comment, let me list all of the extracellular products that have, up to the present time, been identified as substances elaborated by hemolytic streptococci. Some are referred to as toxins, others as enzymes, the difference not always being clearly defined. There are 14 of them as follows: erythrogenic toxin, streptolysin S, streptolysin O, streptokinase, streptodornase (3 different serological types), ribonuclease, hyaluronidase, diphosphopyridine nucleotidase, streptococcal proteinase,—also a proteinase precursor,—amylase, and just recently a so-called fibrinogen precipitating substance. The findings illustrate in an extraordinary way the multiplicity of activities going on in this microscopic bit of unicellular protoplasm.

I could—but I will not—compound confusion on confusion by noting that the synthesis of each of the extracellular products mentioned requires biosynthetic units contained in or on the cell wall of each separate bacterial cell.

Having given consideration to the qualitative features of enzymatic actions of SK and SD, I will now turn to quantitative measurements which have seemed to us to be an essential requirement for proper efforts at enzymatic therapy.

First the streptokinase system. In order to make the points satisfactorily the factors that I will describe concern the intravenous use of SK in a highly purified form in which toxicity has been reduced to a minimum. Although these same types of measurements are applicable to guiding the local use of SK, the i.v. studies more clearly illustrate the problems that have been encountered.

The ultimate lysis of fibrin, as it occurs in vivo through the mediation of SK, invokes a series of steps that indicate a somewhat complicated mechanism. The technical details of

the fibrinolytic phenomenon, as it occurs with and without SK, have been excellently presented in a recent review of the subject in an article by Sherry and associates (2) which has appeared in Physiological Reviews, entitled "Fibrinolysis and Fibrinolytic Activity in Man".

Consumation of the lysis of fibrin through SK has been accounted for by the capacity of SK to transform an inactive substance designated plasminogen into the active fibrinolytic reagent called plasmin. Subsequent studies have complicated the interpretation of the mode of action further by postulating the presence in normal circulating blood of a "proactivator" which SK converts into an "activator", which in turn transforms plasminogen into plasmin which in turn effects lysis.

The measurements which my associates and I, as well as others, have made with specimens of blood from patients, include first the plasminogen content. This figure serves as a basis for determining the amount of SK required for infusion in order to transform all of it into plasmin. Then the determination of the yield of plasmin indicates the amount of fibrinolysin available for eradication of the intravascular fibrin clot.

The measurements are, however, not yet completed. Normal blood possesses an inhibitor to the fibrinolytic phenomenon. In all biological systems, operating in vivo, there is a balance between active agents and inhibitors. The well known continuous homeostasis, so beautifully described by Dr. Walter B. Cannon, depends on this type of balance by which nature controls, within the body, the extent of activities as required, and their inactivation as required.

The amount of nonspecific fibrinolytic inhibitor in patients has been found to vary widely from individual to individual under conditions not yet understood. In planning the optimum dose of SK, therefore, it has been necessary to know how many units of SK will be required to overcome the inhibitor effect in each patient.

Still another practical measurement is required. In our earliest studies of the SK phenomenon, we made the observation that patients recovering from acute hemolytic streptococcus infections developed a specific antibody to SK which nullified the SK-fibrinolytic system. Since antibacterial antibodies of various kinds may exist unsuspectingly in patients, a determination of the titre of specific anti-SK has been necessary for each patient. The dosage of SK was then adjusted to an amount sufficient to satisfy both the antibody as well as the nonspecific inhibitor.

In summary then, the measurements made on each patient were: plasminogen, plasmin, inhibitor, and antibody. From these figures the dosage of SK has been estimated. It may be said in passing that the laboratory procedures required for these determinations, are not unduly technical nor time-consuming, and the results are uniform. The number of units of SK required to yield the maximum amount of fibrinolytic activity within the circulating blood is made with considerable accuracy. These studies dealing with patients, have been published (3, 4), and I need not detail them now, except to mention one or two points. First it was found that a preliminary carefully measured priming dose took care of the inhibitor and antibody. This was followed after a short interval by the infusion of an additional measured amount of SK, which was available to create fibrinolytically active plasmin.

In the report of these studies, it was shown that clots artificially established in a superficial vein of the arm of patients, were effectively liquefied providing the infusion was started within 24 hours of the time of clot formation; if the clot persisted 48 hours prior to the infusion, lysis occurred less completely or reformed; if the clot remained longer, no lysis occurred. It is obvious that more investigation is required of this problem, and I need not extend my remarks further except to point out that the most likely conditions under which SK would be employed in patients should be at the earliest possible moment after acute embolism or thrombosis had occurred. Thus advantage is taken of the time factor mentioned above.

If I have fulfilled my purpose in giving the preceding details, it is to emphasize my point that the development of and advance in any type of enzymatic therapy must get its firm foundation, on, first the specific qualitative actions of the enzyme, and, secondly, on determinations of the quantitative amounts required to fulfill, in vivo, within the patient the purpose of the therapy. It seems to me unlikely that in the highly specialized field of enzymatic therapy, the empirical approach, based on either clinical or statistical estimations of therapeutic results will be profitable.

The number of enzymes employed at the present time in practical therapeutics are quite limited. In addition to our studies, they include trypsin and hyaluronidase. What a meagre representation of the enormous armamentarium of enzymes continually operative in the living processes.

The other streptococcal enzyme to which my associates and I have given considerable study, is desoxyribonuclease, called streptodornase, also SD.

This DNAse, as it exists in the mixture of enzymes called Varidase, is composed of several nucleolytic enzymes, that operate in the following manner. First the DNA-protein is depolymerized by DNAse to nucleotides. Second, the nucleotides are depolymerized by nucleotidases, to nucleosides. Finally the nucleosides are broken down by nucleosidases with the ultimate liberation of free purine bases such as adenine and guanine.

In contrast to SK, the action of SD requires only the presence of Mg^{**} in a concentration of .003 millimole per litre, an amount which is always abundantly present in body fluids and tissues. The actions of SD just mentioned, therefore, are direct upon the substrates and do not require the presence of intermediate or mediating substances.

SD has not yet been available in a purified form. Consequently, its actions, in vivo, have only been observed as it occurs in the mixture SK-SD, designated by Lederle Laboratories as Varidase.

However, DNAse studies have been pursued in patients by employing DNAse of beef pancreatic origin, which is available as a highly purified crystalline entity (Worthington Chemical Co.). It is a single enzyme rather than a series as in the case of the SD contained in Varidase. It depolymerizes DNA-protein only to the level of tetranucleotides. However, this effect changes the physical properties of the protein so that the stringy, viscous quality of DNA-protein is lost, yielding a thin solution.

Without giving complete details of our studies, the special points of interest that have so far emerged from the injection of pancreatic dornase (PD) into patients may be summarized (5, 6). The first observation of special interest was the absence of toxicity. This was true whether the enzymatic solution was given intravenously or by other parenteral routes, including the meninges. As much as 8,000,000 units have been given in a day, which is the equivalent of 88 mgms of protein. Out of several hundred trials, there was one instance of an immediate type of nonfatal allergy. The usual febrile responses referred to as foreign protein types of reaction have not occurred.

Furthermore, this material, even though pure protein and of animal origin, is a very weak antigen, most patients exhibiting no antibody or, when present, only in low titre.

Following the infusion or injection of PD into patients, it was also of special interest to observe that the enzyme diffused in an active form from the blood stream into the serous cavities of the body such as pleura, peritoneum, cerebrospinal canal and into edema fluid. The amount that diffused did not reach the height of the blood level but was in sufficient concentration to exhibit enzymatic activity. A proportion of the PD also appears in the urine in an active form, mediated by a special type of renal clearance. The molecular weight of PD is about 60,000, equal to that of albumin. The mechanism of its diffusion and renal excretion is not yet clear. It seems possible that in contrast to the globular protein such as albumin, PD may exist as thin wiry units,

a shape which makes possible its passage through membranes not similarly penetrated by other proteins of comparative molecular size.

Because of the special features just outlined, we have explored the possible usefulness of PD, injected intravenously and parenterally in the treatment of patients with local purulent infections. Two articles on these studies have been published. One deals with its use in lung abscess (7); the other with its use in the treatment of acute pneumococcal meningitis (8).

Three findings in each of the diseases mentioned may be commented upon.

First, the parenterally injected PD diffused into the area of suppuration and its presence there was biochemically identified. Second, it caused extensive breakdown of the thick viscous pus into a thinner solution. Third, it appeared to be clinically beneficial to the patients by making drainage much more adequate and by permitting the more abundant entrance of leucocytes, antibodies, and antibiotics into the site of disease. The results in pneumococcal meningitis were particularly definite, because, in addition to the other favorable effects, blocks of the cerebrospinal canal which are often the curse of bacterial meningitis were broken up. I might mention in passing that such blocks are spoken of as fibrin blocks. Since purified PD has no fibrinolytic activity it is obvious that deposits of DNA-protein play a significant role in the formation of this mechanical barrier referable to thick viscous materials. Either the blocking material is pure DNA-protein or is a mixture of DNA-protein and fibrin, in which case when DNAse liquefies the DNA-protein present in the blocking material, the matrix, which may also contain fibrin, falls away.

As had been mentioned before in connection with biological principles, where there is an active agent in the body there is also an inhibitor. Such a naturally occurring inhibitor exists for DNAse activity. In contrast to the SK inhibitor previously described, the DNAse inhibitor is uniform among different individuals and is low in titre. In view, therefore of the fact that unusually large amounts of PD can be introduced into the body, it has not proved necessary to take into account either inhibitor or specific antibody when planning the dosage of PD.

One other DNAse should be mentioned. It is the endogenous form normally present in the human body. Its function in all probability is to remove the DNA-protein that is released in the normal cellular turnover. DNA-protein is chiefly derived from the nuclei of cells. In addition, the resolution of encapsulated purulent products, as they occur in local undrained infections, is a slow process based on the limited concentration of endogenous DNAse.

The balance under normal conditions between the amount of endogenous DNAse and its inhibitor again exemplifies the body's homeostatic balance; enough DNAse to take care of the debris derived from the wear and tear of normal cellular disintegration; sufficient inhibitor to restrict excessive enzymatic action.

In the therapeutic use of SK and DNAse, the attempt is made to supply at the crucial site of disease, a great excess of the appropriate enzyme in order to give maximum speed to the rate of breakdown of, on the one hand fibrin, and, on the other hand purulent material. By so doing the imperfections of natural healing referable to the insufficient amount of endogenous fibrinolysin or DNAse, are supplemented so that excessive fibrous tissue formation is prevented or severely restricted. On the basis of this rationale, these particular studies are being continued along well defined lines.

I have now given sufficient findings from the experience of my associates and I to indicate the point of view which we have had toward the problems that they presented. I would like to return briefly in closing to some general comments on the broader topic of enzymes in general for therapy.

For example, with respect to the possibilities of the successful use of purified SK intravenously in the treatment of such diseases

as coronary occlusion or cerebral thrombosis or other disease primarily dependent upon intravascular clot formation, one may justifiably query, is it sufficiently promising to justify vigorous exploration? There are difficulties to be overcome and several aspects of the total problem remain to be solved. Perhaps one can see in the rapid progress of cardiovascular surgery a definitive and successful method of eradicating the damaging effect of occlusive thrombi and emboli by their rapid mechanical removal. It is not my purpose to attempt to resolve the alternatives. For the medical approach to the clot problem, it is difficult to overlook the importance of the two points which I have stressed; namely that fibrin is an insoluble protein, but, under appropriate conditions it can be abolished by rapid dissolution by fibrinolytic enzymes from perhaps a variety of sources. The problems in the regularly successful use of SK are symbolic of the types of problems inherent in many types of enzyme therapy. However, as I stated at the beginning of my talk and reiterate again now, the unparalleled capacity of enzymes to destroy pathological tissues and equally extraordinary ability to restore normal tissue by anabolic actions make the development of their use in treatment a most provocative field to explore.

What I have elaborated upon in advocating the potentialities of many forms of enzymatic therapy is simple to say, but obviously the amount of new knowledge necessary to make such methods available and practicable for the restoration of normal tissue and the eradication of pathological tissue, is very great. However, if diseased tissues and organs could be repaired by such means, perfect forms of therapy would be in prospect.

The total problem of enzymes for therapy is bound up with the balance between the difficulties that must be faced and overcome in relation to the potential benefits that might accrue.

In this connection I would like to recall, in closing, some earlier experiences in another field of therapy. Ehrlich is, I believe, properly referred to as the father of chemotherapy for infective diseases. His persistent search for disinfectants extended over many years and involved the trial of numerous chemical reagents. A moderate degree of success was attained in the local treatment of local infections. But for systemic infections his only success was in the use of arsenicals in the treatment of syphilis.

The problem of chemotherapy had so many difficulties and disappointments that one of his associates, von Behring by name, after ten years study in Ehrlich's laboratory wrote as follows:

"It can be regarded as almost a law that the tissue cells of man and animals are many times more susceptible to the poisonous effects of disinfectants than any bacteria known at present. Therefore, before the antiseptic has a chance either to kill or inhibit the growth of the bacteria in the blood or in the organs of the body, the infected animal itself will be killed. The pessimism of him who declared that disinfection in the living body is for all time impossible appears to be only too justified."

Perhaps if the difficulties inherent in the advancement of enzymatic therapy seem at present too considerable, one might still view optimistically the possibility of future successes in this field by restating again the pessimism expressed in the above quotation from von Behring concerning chemotherapy and in reply say: please pass the penicillin!

COMPREHENSIVE REFERENCES

1. Tillett, W. S.: Studies on the enzymatic lysis of fibrin and inflammatory exudates by products of hemolytic streptococci. Harvey Lecture, **45:** 149, 1952.
2. Sherry, S., Fletcher, A. P., and Alkjaersig, N.: Fibrinolysis and fibrinolytic activity in man. Physiological Reviews, 39, No. 2 (April) 1959.

OTHER REFERENCES

3. Tillett, W. S., Johnson, A. J., and McCarty, W. R.: Intravenous infusion of the streptococcal

fibrinolytic principle (streptokinase) into patients. J. Clin. Invest. **28:** 173, 1949.

4. Johnson, A. J., and McCarty, W. R.: The lysis of artificially induced clots in man by intravenous infusions of streptokinase. J. Clin. Invest. **38:** 1627, 1959.

5. Sherry, S., Johnson, A. J., and Tillett, W. S.: Actions of streptococcal desoxyribose nuclease (streptodornase), in vitro and on purulent pleural exudations of patients. J. Clin. Invest. **28:** 1094–1104, 1949.

6. Johnson, A. J., Goger, P. R., and Tillett, W. S.: Intravenous injection of bovine crystalline pancreatic desoxyribonuclease into patients. J. Clin. Invest. **33:** 1670–1686, 1954.

7. Ayvasian, J. H., Johnson, A. J., and Tillett, W. S.: The use of parenterally administered pancreatic desoxyribonuclease as an adjunct in the treatment of pulmonary abscesses. Amer. Review of Tuberc. and Pulm. Dis. **76:** 1, No. 1 (July) 1957.

8. Johnson, A. J., Ayvasian, J. H., and Tillett, W. S.: Crystalline pancreatic desoxyribonuclease as an adjunct to the treatment of pneumococcal meningitis. New Eng. J. of Med. **260:** 893 (April 30), 1959.

Tranquilizers: Their Use and Abuse[1]

By CYRIL F. CONWAY, JR., M.D.[2]

PERIODS of history invariably become labeled according to the predominant influence of the time, thus the Stone Age, Dark Ages, Renaissance, Industrial Revolution, and now the Atomic Age. It has become quite popular for contemporary society to envision its place in history as that of atom conqueror. On the other hand, however, man's unending battle against his inner-self has reached dramatic proportions so that historians of the future may well label this as the Anxious Era, or even more aptly, the Ataraxic Age.

In 1958, private physicians wrote an estimated 50 million prescriptions for tranquilizers (21). This fact means that more than three out of every ten prescriptions were for ataractic drugs (8). By far, the vast majority of these drugs are employed by the adult population. No one can estimate the actual number of non-institutionalized patients who are actually receiving these drugs, but it can't be denied that a significant segment of the adult population of the United States is taking ataraxics of one type or another at any one time.

The tranquilizers present a medico-social problem not only because of toxicity and side-effects but because they achieve the very effect that is desired, ataraxia or tranquility. In a recent, somewhat philosophical article entitled "Treacherous Tranquilizers" (21), Shaw points out that in general, the ataractic drugs relieve anxiety in mental states where it is present, thus living up to their classification, derived from the Greek "atarax", meaning "peace of mind". An interpretation of this article is that tension is an inborn psychosomatic disorder of men arising from a conflict between innate selfishness and an urge toward gregariousness. Tension properly channeled lights the fire of ambition becoming a positive creative force in which the individual endeavors to become something more positive than he is. Frustration of his ambitious dreams breeds more tension and the fear of frustration, which is called anxiety. Chronic frustration tends toward chronic anxiety in which the individual loses efficiency and eventually, self-respect.

Hence, our ever-accelerating society requires a delicate balance of tension sparking ambition with a minimum of frustration leading to anxiety. The problem here is that the utopia of ataraxia is a land of do-nothing, for without anxiety there is no tension, and a relaxed person is an unambitious person, a luxury which our society can ill-afford in its present state.

In this same paper, the author points out that patients may even become anxious about their lack of anxiety while taking tranquilizers. The question is therefore raised that if anxiety is the match that lights the fire of ambition, are the ataraxics a breeze which may snuff the match? It becomes obvious that improper, or indiscriminate use of these drugs has implications other than the more direct effects subsequently discussed.

To this point, a large group of pharmacologically similar, but chemically unrelated compounds have been referred to as "tranquilizers" and "ataraxics". In doing so, it has been implied that all of these drugs have identical effects and therefore interchangeable. Nothing could be further from the truth. As these drugs have become better known, the indications for the use of specific compounds has become more apparent. The absolute and relative contraindications are much better known than they have been in the past. In other words, the im-

[1] William Harvey Perkins Prize Essay I, College of Physicians of Philadelphia, 1959.

[2] Resident in Obstetrics and Gynecology, Temple University Medical Center, Philadelphia 40, Pennsylvania.

mediate danger to the public lies in the misuse and overuse of these drugs through the ignorance of the physician who prescribes them. If there is any hazard of society proceeding to ataraxia, which is unlikely, it would seem even more likely to be avoidable as only more intelligent application of these tools can be forthcoming.

It is the purpose of this paper to summarize some of the knowledge which is available at the present time concerning these compounds.

PHARMACOLOGY

It is possible to classify the compounds presently in clinical use into two groups, the first according to chemical structure (3, 8, 21) and the second, according to potency.

In general, the tranquilizers fall into four groups according to chemical structure.

1. Rauwolfia serpentina
   - whole root (Raudixin)
   - alkaloid fraction (Rauwiloid)
   - reserpine (Serpasil)
2. Phenothiazine derivatives
   - chlorpromazine (Thorazine)
   - prochlorperazine (Compazine)
   - promazine (Sparine)
   - perphenazine (Trilafon)
   - thiopropazoate (Dartal)
   - mepazine (Pacatal)
   - trifluprometazine (Vesprin)
3. Propanol derivatives
   - mephanesin (Tolserol)
   - meprobamate (Miltown, Equanil)
4. Benzhydrol compounds
   - pipradol (Meratran)
   - azacyclonol (Frenquel)
   - benactyzine (Suavitil)
   - hydroxyzine (Atarax)
5. Miscellaneous compounds
   - phenaglycodol (Ultran)
   - ethylcrotonyl urea (Nostyn)

In general, reserpine, the phenathiazines and benzhydrol compounds have similar properties in that they affect autonomic systems, potentiate barbiturate action and depress conditioned responses (8). Propanol derivatives act by depressing central nervous system interneuron activity in multi-neuron pathways. Their action is upon the thalamus and not the hypothalamus, limbic areas or cerebral cortex (except in large doses). Thus, the propanols have no real effect upon the autonomic nervous system.

In classifying these drugs as to potency, the criterion used is the effectiveness of the compounds in psychotic reactions.

1. Potent anti-psychotic effect—chlorpromazine, promazine, mepazine, perphenazine, prochlorperazine, reserpine.

2. Mild or no anti-psychotic effect—azacyclonol, hydroxyzine, meprobamate, phenoglycodol, ethylcrotonyl urea.

The pharmacology of the ataraxics is little known. In a recent review of the psychopharmacology of the tranquilizers, French (8) sums up what little knowledge is available.

The reticular formation of the brain stem is the principle integrating system of the brain. This area has become known as the nonspecific "Reticular Activating System (RAS)". The functions of the RAS are:

1. *Arousal*—The transitional phase between sleep and wakefulness.

2. *Motor Control.*—As the seat of the extrapyramidal system, the RAS enhances or inhibits motor activity.

3. *Autonomic Balance and Endocrine Control*—mostly through the hypothalamus.

4. *Emotional Stability*—mediated via RAS connections to ancient rhinencephalic areas (hippocampus, amygdala, septal region, limbic cortex).

5. *Sensory Control*—The RAS controls reception and conduction of all sensory signals, accepting or rejecting the sensations crowding toward consciousness.

The physiologic neurohumors of the RAS are carbon dioxide, oxygen, acetyl choline and epinephrine.

Contrary to popular belief in medical circles, the action of general anesthetics is upon the RAS rather than the cerebral cortex. The primary action of excitatory drugs such

as marihuana, peyote, opiates, cocaine and LSD is also upon these areas. Psychotomimetic drugs such as LSD tend to increase sensory inputs into the RAS while tranquilizers tend to decrease RAS function on a semi-selective basis. Amphetamine acts by lowering the threshold of excitability of the reticular formation which results in hyperactivity, sleeplessness, anorexia and euphoria in addition to its adrenergic activity. It is interesting to note that the optical isomer of azacyclonol has properties similar to amphetamine.

The RAS is known to contain large amounts of serotonin. One etiological theory explains psychosis on the basis of deranged neuromediator metabolism, serotonin being a CNS neuromediator. The release of serotonin from body depots including the RAS by the action of reserpine was thought to be corroborative of this theory, however, newer ataraxics show no direct relationship to serotonin. The fact that other serotonin-related compounds such as LSD, mescaline, and yohimbine are psychotomimetic drugs is evidence in support of any theory which may explain psychosis on the basis of disturbance of normal synaptic transmission.

USES

As with any new group of drugs, the tranquilizers have been employed in every medical condition lacking specific therapy. Although the ataraxics were found to be useless in certain areas, they have found places in the treatment of a surprisingly wide spectrum of conditions. A review of the literature shows that certain of the ataractic drugs have properties which aid in the treatment of psychoses and psychoneuroses (those with a large anxiety component), minor motor epilepsy, surgical premedication, narcotic potentiation, behavior disorders, intractable hiccoughing, nausea and vomiting, hypertension, chorea, convulsive states, migraine, drug addiction, alcoholism, porphyria, noctural enuresis, peptic ulcer, ulcerative colitis and certain dermatidites.

It is generally agreed that the main action of this group of drugs is to block the emotional expression of abnormal thought content, however, whether there is any effect upon the underlying psychic turmoil is questionable (7). These compounds lessen emotional tension and conserve physical and psychic energy allowing the patient to reorient himself to reality. Since these drugs do not affect the underlying psychic disorder, their application in any program of mental health may be categorized as prophylactic, adjunctive or as emergency therapy.

1. *Prophylactic*

It has become evident that the majority of emotionally disturbed persons undergo exacerbations of their symptoms rather than having a stable plateau of illness. This is justification for the use of ataractic drugs in the outpatient care of psychoneurotics who are experiencing increased anxiety or free-floating anxiety attacks due to a temporary increase in psychic tension. The family physician is quite capable of administering this type of ataractic therapy if he realizes that it is only a temporary stop-gap type of treatment which permits him to utilize superficial psychotherapy, with or without environmental manipulation, to restore the patient to his usual state of borderline psychic balance. Long-term use of these drugs or misuse through misunderstanding their potentialities and indications is not to be condoned. As with any drug, the physician must be familiar with the limitations of accomplishment. Borderline psychotics and rehabilitated psychotics of a non-depressive type may also be temporarily controlled in times of stress with ataractic therapy. Again the physician must realize what part of the syndrome he is treating and be familiar with the compounds which will accomplish the specific requirements of the moment.

2. *Adjunctive therapy*

This type of therapy is so designated to denote that although these drugs may be

employed in the treatment of in-patient psychotics, they will not cure the disease. These drugs are only of benefit when combined with other therapies. Although the more potent tranquilizers are effective in schizophrenics (6), rendering them less emotionally tense and anxious and more cooperative, one must also realize, in evaluating any drug in the treatment of this group of patients, that approximately 18% of the patients will get well without specific therapy. In a review of the use of chlorpromazine and reserpine in neuropsychiatry (7), Freeman states that 22% of the patients responded well to reserpine, 34% to chlorpromazine and 29% to EST with 18% responding to "last-resort" lobotomy. The author states that of the schizophrenics, 54% of the paranoids, 37% of the catatonics and 33% of the hebephrenics responded to tranquilizers. There was an overall relapse-rate of 33%. He also feels that the ideational content of schizophrenic thinking is affected by the drug as well as the reaction to the abnormal ideation.

Certain groups of patients with other types of abnormal behavior also require adjunctive ataractic therapy (14, 23). Harris and Rowley (9) reported reserpine to be effective in allaying tension in a group of 42 cerebral palsy patients and to be especially beneficial in tension-athetoids and tremor-athetoids. Carter and Maley (4), in a study of mental defectives, found chlorpromazine helpful in reducing abnormal behavior and excitement, thus facilitating training. Bonafedo (2) discussed the use of chlorpromazine in the treatment of 165 disturbed epileptics, the majority being mentally defective, having episodes manifested by irritability, excitement states, temper outbursts, furor states, restlessness, overactivity, resistiveness, destructiveness, assaultiveness, nakedness, selfmutilation, profanity, night wandering, filthy habits and active psychotic trends. The anticonvulsant therapy was maintained in all cases. Livingston (16) found meprobamate an effective adjunct in the treatment of minor motor epilepsy, but of no significant benefit in major motor, petit mal or psychomotor seizures.

3. *Emergency therapy*

Emergency therapy is the use of ataraxics in episodes of extreme psychomotor excitement. In a study conducted at the District of Columbia General Hospital which included 5000 patients (20) in acute psychotic states (eg. manic excitement), severe non-psychotic psychomotor agitation (eg. severe anxiety reaction), organic delirium (eg. delirium tremens), organic tension states (eg. senile tension states) and neurotic tension states (eg. alcoholism), the ataraxics were found to be superior to and more efficient than previous therapy which included sedation (barbiturates, paraldehyde, chloral hydrate), hydrotherapy, wet packs and a drying-out period of several days.

Figures 1 and 2 represent an effort to set forth, in tabular form, the drugs of choice in specific situations presently considered to be indications for ataractic therapy. References 8, 13 and 21 are of particular interest in this regard.

Chlorpromazine, although not superior to reserpine in the treatment of functional and organic psychoses, provides quicker results and is the drug of choice on this basis. Azacyclonol seems to have some specificity in acute hallucinatory reactions which may occur in senile dissociation, post-operatively, or in alcoholism. Meprobamate, prochlorperazine, perphenazine, trifluprozine and phenaglycadol are about equally effective in anxiety neurosis and psychosomatic conditions including dermatitis, allergy and gastrointestinal disturbance. Meprobamate is probably the drug of choice in most psychoneurotic conditions due to its low toxicity, absence of autonomic side effects and its ability to relieve neuromuscular tensions directly. Hydroxyzine is purported to be more effective than the others in temporary emotional stress situations such as overwhelming grief.

SIDE EFFECTS AND TOXICITY

As would be expected from such a large group of drugs which have actions upon many organ systems, numerous side effects and toxicities have been observed. The side effects have been categorized as follows:

1. *Organic Side Effects*

anorexia
convulsions
dermatitis
dizziness
drowsiness
edema
eye symptoms
fatigue
flushing
gastrointestinal
generalized tremulous movements
hypotension
impotence
jaundice
lactation
menstrual irregularities
midbrain syndrome
muscular symptoms
nasal stuffiness
Parkinsonism
ptyalism
reduced resistance to disease
thirst
toxic syndrome
urinary frequency
voracious appetite

2. *Psychological Side Effects*

agitation, depression, insomnia, nightmares, retardation, turbulence
ahedonia, eroticism, lethargy, restlessness, suicide, withdrawal

FIGURE 1

	Anxiety Tension	Alcoholism	Psychosomatic Illness	Reactive Depression	Obsessive Compulsive	Conversion Reaction	Manic Depressive	Hypermanic Behavior	Senile Psychosis	Schizophrenia	Agitated Paranoid	Nausea & Vomiting
Potent Anti-psychotic Effect												
Chlorpromazine (Thorazine)	X				X	X	X	XXX	XXX	XXX		XXX
Promazine (Sparine)	X	X						XX	XX	XX	XX	
Mepazine (Pacatal)	X							XX		XX		
Perphenazine (Trilafon)	XX							XXX	XXX			XX
Prochlorperazine (Compazine)	XXX							XX	XX	XX		XX
Reserpine (Serpasil)	XX		X					XXX	XXX	XX		
Mild Anti-psychotic Effect												
Triflupromazine (Vesprin)	XXX											
Azacyclonol (Frenquel)	X	X								X		
Hydroxyzine (Atarax)	XXX		X	0		0						
Meprobamate (Equanil)	XXX	X	X	X	X				XX	X		
Ethylcrotonyl urea (Nostyn)	XXX	0					0	0	0	0		
Phenaglycocol (Ultran)	XXX	0	XX	X				0		0		

Code: blank—little or no value; 0—contraindicated, X—slight improvement; XX—moderate; XXX—excellent.

FIGURE 2

(from Schultz (20))

Drug	Severe Psychomotor Agitation	Organic Delirium	Organic Tension States	Acute Psychotic States
Chlorpromazine	2	2		2
Promazine	1	1	1	1
Prochlorperazine			5	
Mepazine	3			3
Reserpine	4		4	
Meprobamate			2	
Hydroxyzine			3	

Acute psychotic states	catatonic excitement manic excitement agitated depression
Severe psychomotor agitation (non-psychotic)	homosexual panic severe anxiety reaction borderline psychotic state
Organic delirium	delirium tremens acute toxic disturbances epileptic furor
Organic tension states	senile tension states post traumatic excitement mental deficiency with excitement

As can be seen from this impressive list, the side effects are numerous, moreover each drug has its particular group of drug reactions. Because of the variety of reactions which may be seen, the physician must exercise constant supervision over the administration of these drugs and suspect them when any unusual signs or symptoms appear.

Every physician should be aware of the more serious specific reactions he may encounter and must check his patient at frequent intervals for signs and symptoms of the particular toxicity.

In a recent review of the subject of toxicity, Hollister (10) categorized these specific drug reactions of a more serious nature.

1. *Chlorpromazine*

a. Agranulocytosis—about 50 cases reported—mostly in females over 50 years (only 6 patients under 50 years) Two other phenothiazines have been reported as responsible for this condition, Promazine (2 cases), Mepazine (1 case).

b. Jaundice—One to three per cent of those receiving the drug for more than a week will evidence jaundice due to a cholangiolitic hepatic obstruction. 50% of the patients receiving the drug for several days show changes in liver function tests, particularly alkaline phosphatase. (22) The vast majority of cases evidencing jaundice lose it shortly after the withdrawal of the drug with no measurable residual hepatic damage. Severe liver damage and death have been reported as a rare complication of jaundice. Promazine (12) and mepazine (13) have been reported as having caused occasional jaundice but the validity of these reports is questionable.

2. *Prochlorperazine*

A Parkinsonian-like syndrome of enhanced extrapyramidal system activity is not infrequently observed in varying degree when large doses are given or with long-term administration of the drug. The other phenothiazines have this property to a lesser extent.

3. *Reserpine*

Psychic depression is frequently observed after a few weeks of reserpine therapy and must be anticipated. Removal of the drug is followed by remission of the symptoms after several days. The patient may then be continued on lower doses under close supervision. Depression may become very severe if the drug is continued in its presence. Suicides have been reported. Extrapyramidal tract symptoms may also be seen with reserpine therapy. The symptoms disappear upon removal of the drug.

4. *Meprobamate*

Reports of withdrawal symptoms (6, 15) upon discontinuance of this drug have become increasingly frequent. In a controlled study, Ewing and Haizlip (6) showed that withdrawal

of the drug after 40 days administration of large doses (3.2–6.4 Gm. daily) of meprobamate, 44 of 47 patients developed some symptoms of abstinence. Three patients had grand mal seizures and eight patients exhibited hallucinosis with marked anxiety and tremors. The withdrawal syndrome most frequently observed included several of the following: anorexia, insomnia, vomiting, tremors, muscle twitching and ataxia.

5. *Perphenazine*

Berry (20) reported two cases of cataleptic reaction to this drug in children. Other cases are appearing in the literature. The patients recover after the drug is withdrawn.

Toxicity is not the only problem which faces the physician who treats outpatients with tranquilizers. Regardless of the so-called specificity of these drugs, they do depress mental function and reaction to sensory stimuli. In an interesting study using elaborate equipment simulating automobile driving situations which can be measured quantitatively, Loomis and West (17) found that chlorpromazine in doses of 50 milligrams given twice at five hour intervals impaired function as tested up to 70%. Meprobamate showed significantly decreased function to a lesser magnitude. Neither drug decreased function to the degree obtained after barbiturate administration.

SUMMARY

An effort is here made to clarify the subject of tranquilizers. The potential hazards of an "ataractic society" are briefly touched upon. Following a synopsis of psychophysiology and psychopharmacology, the tranquilizers presently employed clinically are categorized by chemical structure and according to relative potency. The uses and contraindications to the use of the various drugs are summarized. General drug reactions and side effects are enumerated and specific toxicities of certain ataraxics are outlined.

BIBLIOGRAPHY

1. Berry, R. V., Kamin, S. H., and Kline, A.: An unusual complication following the use of Trilafon in children. U. S. Armed Forces M. J. **9:** 5: 745–50, May 1958.
2. Bonafedo, V. I.: Chlorpromazine (Thorazine) treatment of disturbed epileptic patients. AMA Arch. Neur. Psychiat. **77:** 3: 243–6, March 1957.
3. Burbridge, R.: Toxic effects and misuse of tranquilizing drugs. Ann. Int. Med. **49:** 1: 17–29, July 1958.
4. Carter, C. H., and Maley, M. C.: Chlorpromazine therapy in children at the Florida Farm Colony. Am. J. Med. Sc. **233:** 2: 131–6, Feb. 1957.
5. Cone, T. E., Jr.: Promethazine suppositories for management of nausea and vomiting in children. A.M.A. J. Dis. Child. **95:** 397–400, April 1958.
6. Ewing, J. A., and Haizlip, T. M.: A controlled study of the habit forming propensities of meprobamate. Am. J. Psych. **114:** 835, March 1958.
7. Freeman, H.: A critique of the tranquilizing drugs, chlorpromazine and reserpine in neuropsychiatry. N. England J. M. **255:** 877–83, Nov. 8, 1956.
8. French, J. D.: Drug actions upon the brain; psychopharmacology. Annual Rev. Med. **9:** 333–46, 1958.
9. Harris, R. D., and Rowley, E. H.: Reserpine in cerebral palsy. J. Pediat. **49:** 398–400, Oct. 1956.
10. Hollister, L. E.: Allergic reactions to tranquilizing drugs. Ann. Int. Med. **49:** 17–29, July 1958.
11. Jabbour, J. T., Scheffield, J. A., and Montalvo, J. M.: Severe neurological manifestations in four children receiving Compazine (prochlorperazine). J. Pediat. **53:** 153–9, Aug. 1958.
12. Kemp, J. A.: Jaundice occurring during the administration of promazine. Gastroenterology **32:** 5, May 1957.
13. Kurtz, P. L.: The current status of the tranquilizing drugs. Canadian M. Assn. J. **78:** 209–15, Feb. 1958.
14. Lane, G. G., Huber, W. G., and Smith, F. L.: The effect of chlorpromazine on the behavior of the disturbed child. Am. J. Psychiat. **114:** 937–38, April 1958.
15. Lemere, F.: Habit forming properties of meprobamate. A.M.A. Arch. Neur. Psychiat. **76:** 205–6, Aug. 1956.
16. Livingston, S., and Pauli, L.: Meprobamate in the treatment of epilepsy of children. A.M.A. J. Dis. Child. **94:** 277–81, Sept. 1957.
17. Loomis, T. A., and West, T. C.: Comparative sedative effects of a barbiturate and some tranquilizer drugs on normal subjects. J. Pharm. Exp. Ther. **122:** 525–31, April 1958.
18. McClendon, S. J.: Management of nocturnal

enuresis in childhood. Arch. Pediat. **75:** 101–5, March 1958.

19. Miksztal, M. W.: Chlorpromazine (Thorazine) and reserpine in residential treatment of neuropsychiatric disorders in children. J. Nerv. Ment. Dis. **123:** 477–79, May 1956.

20. Schultz, J. D.: The ataraxics in general hospital practice. Symposium at District of Columbia General Hosp., Washington D. C., 1958.

21. Shaw, C. C.: Treacherous tranquilizers. Am. J. M. Sc. **237:** 141–50, Feb. 1959.

22. Shay, H, and Siplet H.: Study of chlorpromazine jaundice, its mechanism and prevention. Gastroent. **32:** 571–91, April 1957.

23. Tarjan, G., Lowery, V. E., and Wright, S. W.: Use of chlorpromazine in two hundred seventy-eight mentally deficient patients. AMA J. Dis. Child. **94:** 294–300, Sept. 1957.

24. Vogele, G. E., and May, R. H.: Epileptiform seizures under promazine therapy. Am. J. Psychiat. **113:** 655–6, Jan. 1957.

Mark Akenside: Eighteenth Century Physician-Poet[1]

By HERBERT J. DIETRICH, JR., M.D.[2]

MARK AKENSIDE'S life (1721–1770) spanned roughly the middle years of the eighteenth century; and was rather unique among the class of poet-physicians in that it produced lasting contributions to both Medicine and Poetry. Oliver Goldsmith, a contemporary of Akenside and a physician, was one of the shining lights of 18th century English Poetry; but his attainments as a physician were meagre indeed. John Keats, born near the end of the century, qualified to practice, but his frail health and untimely death at the age of 26 allow us merely to speculate what might have been the benefits to Medicine of a longer and more robust life. As it was, he achieved immortality through his poems and would have to be included in any list of the half-dozen greatest lyric poets of all times. But Mark Akenside pursued, side by side, the careers of Medicine and Poetry, never seeming to neglect for long his interest in either one. He made definitive contributions to each, so that of the poet-physicians he alone might deserve to be called, as he was by William Cowper, "the two-fold disciple of Apollo"!

Born November 9, 1721 at Newcastle-upon-Tyne, Mark was the second son of a "respectable butcher". When he was seven years old, in his father's shop on the Butcher Bank, a meat cleaver fell upon his foot and "halted him for life". This misfortune is thought by some to have influenced greatly the course of his life and personality. It left him with a pitiful limp which in later years was partially overcome by the use of a lift in the heel of his shoe, enabling him to get about more easily. His early schooling was taken at a local private academy where he was prepared for the ministry. At 18 he went to Edinburgh where his tuition was subscribed by the members of a "dissenting" congregation, Akenside's parents being of Northumberland Presbyterian background. After one term there, however, Akenside himself dissented from further theological education of any sort and withdrew from this course. Already he had begun to write verses. He published his first poems in 1740, and from the sale of them he refunded to the "dissenters" the money they had advanced for his tuition. One of his biographers had said of Akenside at this juncture: "He had begun to climb Parnassus and could not encumber himself with the small clothes of theology nor wear the fetters of the sects". It is not to be supposed, however, that this break with a formal theological education, marked in any way for his future life a lack of religious faith. It did not. Indeed, all of Akenside's poetical works attest to a strong moral philosophy, continued inquiry into the nature of Beauty, Virtue, Truth and Nature. Although it is true, I think, that his works show more the influence of Plato and Deism (or the Religion of Nature) than perhaps of Christian Theology. One wonders whether this accounts in part for one criticism of his poetry when it is described as "lacking the essential fire and warmth of genius".

In 1739 Akenside began, at Edinburgh, the study of medicine and was elected a member of the recently formed Student Society, the now famous and historical Royal Medical Society of Edinburgh. His participation in the debates of the Society gave Akenside an opportunity to exercise his talents of eloquence and literary knowledge. He remained at Edinburgh for

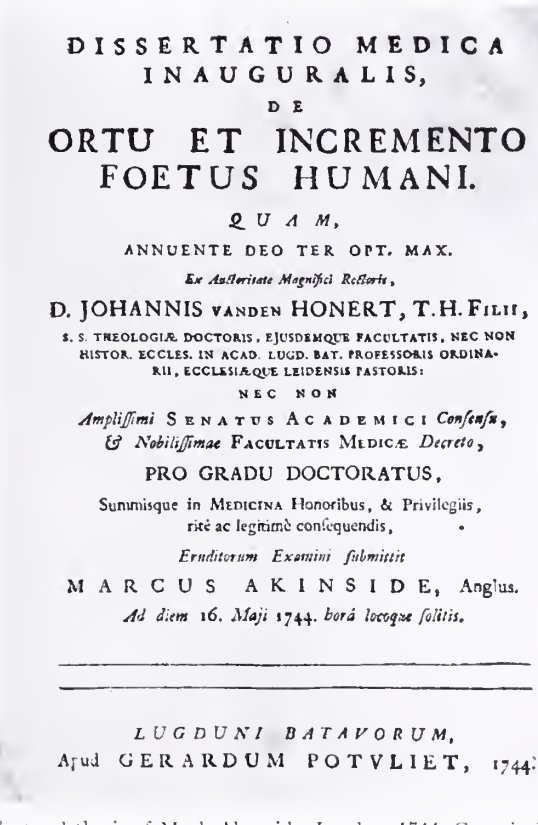
[1] Read before the Section on Medical History, College of Physicians of Philadelphia, 17 February 1959.

[2] Chairman, Section on Medical History.

about eighteen months; and despite his literary distractions, he apparently acquired enough medical knowledge to feel competent as a practitioner.

Accounts now differ as to the exact course of his next few years. According to some, Akenside began practice in Newcastle, possibly even from the somewhat inappropriate address, the Butcher Bank. Other accounts indicate that he was busy composing "The Pleasures of Imagination", the moral philosophical poem (in three books) upon which his fame as a poet mainly rests. These same accounts relate that after a short time in London he went on to Leyden, acquiring there his medical degree in six weeks' time. Contrary to these accounts, and perhaps more authoritative is the one left to us by Samuel Johnson in his *Lives of the Poets*: "In 1741 he [Akenside] went to Leyden, in pursuit of medical knowledge; and three years afterwards (May 16, 1744) became Doctor of Physic, having according to the custom of the Dutch universities, published a thesis or dissertation. The subject was, 'The Origin and Growth of the Human Fetus', in which he is said to have departed, with great judgment, from the opinion then established, and to have delivered that which has since been confirmed and received."

In this monumental work, "The Origin and Development of the Human Fetus", is to be found a very exacting description of the anatomy of the generative organs of the human female, ideas about the fertilization of the ovum, placentation, nourishment of the fetus via the umbilical circulation. The work is in thirty-nine paragraphs, printed in Latin, of which I have translated a part; the work, so far as I know, not having appeared in English



DISSERTATIO MEDICA
INAUGURALIS,
DE
ORTU ET INCREMENTO
FOETUS HUMANI.
QUAM,
ANNUENTE DEO TER OPT. MAX.
Ex Auctoritate Magnifici Rectoris,
D. JOHANNIS VANDEN HONERT, T.H. FILII,
S. S. THEOLOGIÆ DOCTORIS, EJUSDEMQUE FACULTATIS, NEC NON HISTOR. ECCLES. IN ACAD. LUGD. BAT. PROFESSORIS ORDINARII, ECCLESIÆQUE LEIDENSIS PASTORIS:
NEC NON
Amplissimi SENATUS ACADEMICI *Consensu,*
& Nobilissimae FACULTATIS MEDICÆ *Decreto,*
PRO GRADU DOCTORATUS,
Summisque in MEDICINA Honoribus, & Privilegiis,
ritè ac legitimè consequendis,
Eruditorum Examini submittit
MARCUS AKINSIDE, Anglus.
Ad diem 16. *Maji* 1744. *horâ locoque solitis.*

LUGDUNI BATAVORUM,
Apud GERARDUM POTVLIET, 1744.

FIG. 1. Title page of doctoral thesis of Mark Akenside, Leyden, 1744. Copy in Library of the College of Physicians of Philadelphia.

before this. The following is a translation of the third paragraph:

> In this definite duplication of the broad ligament, as has been mentioned, adhere the two ovaries and the subserving Fallopian tubes. The ovary occupies the uppermost part of the ligament on each side; a small mass, rather oval, spongy and whitish, situated at a distance of about two fingers from the uterine fundus to the angle of which, with a short intervening space, it is nevertheless joined by a strong ligament. Its structure comprises fascia, nerves, blood-vessels and lymphatics; these enfolded and interwoven in a wonderful way, give rise to various interstices and thus furnish space and room for the small seed-vessels, spherical and transparent, which the more recent anatomists have given the term 'eggs'. These are invested with a double membrane. They swell—tense with fluid—in the presence of heat, and adhere to certain particular depressions which might indeed be called the "cups" of the eggs. In fact, a tough fibrous membrane invests the whole surface of the ovary, perforated by tiny foramina rendered more open at the time of conception, and provide for the exit of the egg from the ovary so that it may be carried down the Fallopian tubes. Just how this occurs is to be explained more fully below.

Obviously this thesis is not the result of six weeks' work, but more likely required several years of anatomical dissections and observation. If it is more beautifully descriptive than the usual anatomy book, it is nevertheless accurate and represents an original and permanent landmark in the knowledge of the subject.

Interestingly, it was in the same year as his Leyden thesis that Akenside's poetical magnus opus, "The Pleasures of Imagination", was published. About it Samuel Johnson has the following to say: "I have heard Dodsley, by whom it was published, relate, that when the copy was offered him, the price demanded for it, which was an hundred and twenty pounds, being such that he was not inclined to give precipitately, he carried the work to Pope, who, having looked into it, advised him not to make a niggardly offer; for 'this was no everyday writer'." *The Pleasures of Imagination* has since been looked upon as one of the most excellent examples we have of blank verse in English. Akenside's contemporaries regarded it in this respect as second only to the genius of Shakespeare. In addition to "The Pleasures . . . ," he composed about thirty-three odes, in two books, and some hymns. In his "Hymn to the Niads" he came very near to recapturing the spirit of the Pindaric ode. There are several Epistles and a few miscellaneous poems of which one of the most charming is his "Hymn to Science". In later life Akenside embarked upon a revision of his greatest work, "The Pleasures . . .", but it was never finished. According to Saintsbury it showed signs of "a second Spring".

Upon his return from Leyden to England, Akenside began to practice in Northampton, but without noteable success. He was then twenty-three years old. His friend and patron, Mr. Jeremiah Dyson, rescued Akenside and gave him a house and an allowance in the North End of London, where likewise his practice was not promising. He then moved to Bloomsbury, aided again by Dyson, and there was for the first time successful in the practice of medicine. From then onward his rise was rapid and sure. He became a fellow of the Royal College of Physicians in 1753. He was twice a censor of the College between 1755 and 1760, and at various times an examiner of candidates for the Fellowship. Meanwhile he had been admitted (by mandamus) to the degree of Doctor of Physic, Cambridge University. He was soon called upon to deliver, at different times, two of the endowed series of lectures of the College, the Goulstonian and the Croonian. On October 18, 1759, at the age of 38, he delivered the Harveian Oration. "At the College of Physicians", one biographer says, "he was diligent in his attendance at the quarterly comitia; and discharged his duties with satisfaction, and those requiring the literary graces—with every possible distinction." On February 8, 1754, at the age of 32, he was elected into the fellowship of the Royal Society.

In time Doctor Akenside acquired considerable reputation and practice. He obtained his first hospital appointment in 1759 when he became assistant physician to both Christ's and St. Thomas's hospitals. Within three

months of his joining the latter hospital he was appointed physician. In 1761 he became one of the three physicians to the Queen. In 1762 he moved to Old Burlington Street, the then Harley Street of London, where a number of his colleagues at the College of Physicians conducted their practices. His life from then on assumed a more or less set pattern, year in and year out: attendance at the Comitia, a modicum of private practice, regular attendance at St. Thomas's, the meetings of the Royal Society, and the rounds of the coffee houses near Charing Cross,—these being a necessary adjunct to the Royal Society.

Akenside's medical writings before his appointment at St. Thomas's are mainly academic in character; those after his appointment are, with rare exception—clinical. The Goulstonian Lectures, first given before the Royal College of Physicians in 1755, were repeated two years later for the Royal Society. Their title was: "Opinions on the Lymphatic Vessels." Akenside may be fairly regarded among the first to have described clearly and correctly the function of the lymphatics. His Harveian Oration in 1759 was entitled: "On the Effects of a Blow to the Heart." Other medical writings include: "De Dysenteria Commentarius" and "Observations on Cancers".

Akenside, the man, was apparently very popular with his fellow physicians and fellow literateurs; but most of the records indicate a certain lack of humanity in his dealings with his patients. He was apt to be petulant and arrogant, and wanting, from time to time, in good manners. Yet we are told that he was one of the most followed physicians on the wards of St. Thomas's.

From the relatively few available facts concerning the life of an obviously complex man, a physician, a poet, bordering on genius, we can reconstruct part of the picture. For the rest one must rely on the writings of the man himself, both medical works and poetical. In spite of some of the less attractive facets of his personality, he was a man of great intellectual integrity, with a vast amount of learning, all of which he placed at the disposal of his fellow man and human institutions, and in so doing found his own life rewarding and enjoyable. His life was to end all too soon, at the age of 49, from what appears to have been septicemia following a severe throat infection. He died June 23, 1770, in the bed of John Milton which had been given to him as a gift in 1761. He was buried five days later in St. James's Parish Church, Westminster. The following two stanzas from his "Hymn to Science" are a fair sample of his poetry and tell the sort of man he was, poet and physician.

"Raise me above the vulgar's breath,
Pursuit of fortune, fear of death,
And all in life that's mean:
Still true to reason be my plan,
Still let my actions speak the man,
Through every various scene."

"Sun of the soul! thy beams unveil:
Let others spread the daring sail,
On Fortune's faithless sea:
While, undeluded, happier I
From the vain tumult timely fly,
And sit in peace with thee."

Memoir of William C. Stadie (1886–1959)*

By ISAAC STARR, M.D.

BORN in 1886, Dr. William C. Stadie was in his adult days older in years than in medicine, because lack of funds delayed his education, and he was forced to teach school for some time before he could enter medical college. Still pressed for funds as an undergraduate at the College of Physicians and Surgeons, he was fond of relating how he financed his studies by writing a text book of Pathology; if surprise was expressed as so important an accomplishment by so young a man, one quickly learned that he had the job of typing the original manuscript of McCallum' well-known book on that subject.

After serving an internship in the Presbyterian Hospital in New York, Stadie went to the Hospital of the Rockefeller Institute and almost at once was precipitated into an urgent research, for the great influenza pandemic of 1918 had raged through the country and conventional efforts to combat the intense cyanosis and terrible mortality had proved futile.

Today, with large parts of the University Hospital piped for oxygen and with arterial puncture and blood-gas analysis routine procedures, one wonders how many of the interns and staff could tell where and how such methods originated. Oxygen had been administered long before Stadie's time by the totally inadequate method of dangling a tube before the patient's nose; a German had punctured an artery before Stadie did. But, it was Stadie who built up the first truly effective method of administering oxygen to patients, in a specially constructed room in Rockefeller Hospital, and it was he who first employed arterial puncture for a useful purpose. The standard blood-gas analyser of Van Slyke was, until very recently, shaken by a simple apparatus Stadie devised. So it was in large measure the result of Stadie's skill that cyanosis in pneumonia was quantitatively evaluated for the first time, and that effective oxygen therapy was made possible. Such therapy has been in use ever since, throughout the world.

After a brief period on the faculty at Yale, Bill Stadie came to the University Hospital as Associate Professor of Research Medicine in 1924, and he was promoted to Musser Professor of Research Medicine in 1941.

Always endowed with the quantitative viewpoint, and with unusual facility in mathematics, at the time of his arrival at the University, Stadie was far ahead of the majority of the faculty in this regard. For several years he continued to work with the techniques of blood-gas analysis which he had mastered in Van Slyke's laboratory. Then he suddenly was made aware of a large quantitative discrepancy in the available data of a well-known physiological process, which everyone thought to be perfectly understood. Much more CO_2 came out of the blood in its passage through the lungs than the current views of the physical chemistry of blood would account for. The search for an explanation led him into a new field, that of the enzymes. To explore this field, new techniques were necessary, those of enzyme chemistry to measure enzyme activity, and those relating to radioactivity to locate the enzyme in tissue and to identify the source of its metabolic by-products. These new techniques were mastered, and by such means Stadie made major contributions to our knowledge of the metabolic abnormalities which manifest themselves as diabetes mellitus, and of the action of insulin upon them. As a result of these studies our conceptions of the underlying abnormalities of diabetes have been

* Read before the College of Physicians of Philadelphia, 3 February 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

greatly altered, and Stadie's work is everywhere accepted as the last word on this subject.

Indeed, throughout his active years, as he approached retirement, and even after he had become emeritus, he never showed any sign of the mental rigidity which so often comes with age. In his later years, despite considerable ill health, some of it of a painful character, his mind remained every bit as active and as fertile for new ideas as in his younger days.

The quality of the man and of his work was recognized everywhere. He was an editor of the Journal of Biological Chemistry for many years, and Editor-in-Chief of "Diabetes" during the three years which preceded his death. He received the Phillips Medal of the American College of Physicians in 1940; the Kober Medal of the Association of American Physicians in 1955; the Banting Medal of the American Diabetes Association in 1956; and the Alvarenga Award of this College in 1957. He was a member of the National Academy of Sciences, the American Philosophical Society and he received the Honorary Degree of Doctor of Science from the University of Pennsylvania in 1959.

Any tribute to his unusually successful scientific career must be accompanied by an equal tribute to Bill Stadie as a friend and as a man. A poor boy himself, he had keen interest in all social problems and great sympathy for the downtrodden. He had a host of friends; I never heard of an enemy, or of anyone who even thought of him as a rival. He ran a happy and successful laboratory, as his many associates, graduate students and technicians are glad to testify. His home life was equally happy, as those of us who were made welcome there know well. Such things do not take place by accident or chance.

Those of us visiting his home often paused to admire the beautiful pieces of mahogany furniture, made by himself in his leisure time with such evident artistry and craftsmanship. Good music delighted him; he played the cello and the clarinet, not well, but well enough to enjoy it. And outside the house stood his garden and his row of beehives.

The death of his first wife, Amanda Brugger, after a lifetime of happiness together, was a cruel blow, but he recovered from it. His second marriage, to Catherine Tyler, though unfortunately brief, was equally happy.

After having suffered from angina pectoris occasionally for many years, he died suddenly, as he would have wished, and at a time when his mental powers were undiminished. His work which so much advanced the fields in which he concerned himself will live long after him.

Memoir of Edward A. Strecker (1887–1959)*

By KENNETH E. APPEL, M.D.

CLINICIAN, Teacher, Researcher, Author, Public Servant, Friend of Physicians, Psychiatrists and his Fellow Men.

Dr. Edward A. Strecker died at Jefferson Hospital on January 2, 1959 after an illness of several months. He was 72 years of age. He was one of the most eminent psychiatrists of this country.

To few men has it come to receive such honors. Consultant to President Franklin D. Roosevelt and a presidential citation from President Harry S. Truman; Consultant to the Army, Navy and Air Force in World War II, the United States Public Health Service and the Veterans Administration; Recipient of many awards including The Salmon Lectureship. He received many honorary degrees: Sc.D. (St. Joseph's), Litt.D. (La Salle), LL.D. (Franklin and Marshall), L.H.D. (St. Bonaventure).

Four medical colleges he served as Professor: Jefferson, 1925–31; Yale, 1925–30; University of Pennsylvania, 1931–53; Seton Hall, 1953–55.

Dr. Strecker's honors came as a result of distinguished achievements. He was a perceptive, penetrating, kindly clinician. At one time he had the largest psychiatric practice in the country. His ability to reach the heart of etiologic and dynamic factors readily and make constructive recommendations for treatment made him not only a skilled diagnostician but a most effective therapist. He was a superb teacher. He cut through complexities and details, the mysterious, unknown and exotic. He put his clarifications and therapeutic recommendations into colorful language which made the memory of the clinical picture interesting and unforgettable. His lectures were so popular, drawing also from the four other medical schools of the city, that tickets of admission had to be obtained.

One of the earliest researches was on 'Recoverable Dementia Praecox Reactions'. This, with the work of Adolph Meyer, Bleuler and Freud, turned psychiatry from the pessimism of heredity and constitution to the optimism of psychological and social factors, both etiologically and therapeutically considered. His therapeutic meliorism was experienced in World War I in which he had a distinguished record treating "Shell-Shock" and other psychiatric conditions. He served as the only division psychiatrist throughout the entire war.

He was one of the first psychiatrists to move out of the mental hospital into the community. Before World War I he was staff psychiatrist of the Pennsylvania Hospital for Nervous and Mental Diseases. Following the war he extended his activities to the general hospital at Eighth and Spruce Streets, where he established one of the first out-patient clinics in psychiatry in the world. Here he stimulated a great deal of interest and work in child guidance.

Dr. Strecker was a prolific writer, having written or authored ten books and over two hundred articles.

He was graduated from La Salle College in 1907, Jefferson Medical College in 1911, interned at St. Agnes Hospital, Philadelphia, and took his residency at the Pennsylvania Hospital in West Philadelphia. His associations were long and deep with the Pennsylvania Hospital. He lived at the West Philadelphia division from the time of his residency until his death.

Dr. Earl Bond and Dr. Strecker were for years closely associated. At the Pennsylvania Hospital and the University of Pennsylvania they together trained more psychiatrists who

* Read before the College of Physicians of Philadelphia, 3 February 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

have attained professorial rank throughout the country than have come from any other psychiatric center. Dr. Strecker was honored by the Presidency of the American Psychiatric Association at its Centenary in Philadelphia in 1944.

Dr. Strecker combined the art and science of psychiatry with a rare keenness, compassion, humor and humanity. It was a great privilege to have been closely associated with him, as his many colleagues and students throughout the country constantly testify. He was interested not only in the care and treatment of patients but he cared for them as human beings. And this came from a warm, optimistic religious feeling, deriving from the training in liberal Roman Catholicism in his home. He added not only to the lustre of his speciality but to medicine, in his university, community and country.

His widow, the former Elizabeth Walsh, died November 19, 1959.

The spirit of Edward Strecker, as I knew him over many years, is so well expressed by William Faulkner in his address on receiving the Nobel Award, that I would like to share it with you.

"I feel that this award . . . made to my work—a life's work in the agony and sweat of the human spirit, not for glory and least of all for profit, but to create out of the materials of the human spirit something which did not exist before. . . . I would like to use this moment as a pinnacle from which I might be listened to by the young men and women already dedicated to the same anguish and travail. . . .

Our tragedy today is a general and universal physical fear so long sustained by now that we can even bear it. There are no longer problems of spirit. There is only the question: when will I be blown up? Because of this, the young man or woman writing today has forgotten the problems of the human heart in conflict with itself which alone can make good writing because only that is worth writing about, worth the agony and the sweat.

He must learn them again. He must teach himself that the basest of all things is to be afraid; and, teaching himself that, forget it forever, leaving no room in his workshop for anything but the old verities and truths of the heart, the old universal truths lacking which any story is ephemeral and doomed—love and honor and pity and pride and compassion and sacrifice. Until he does so he labors under a curse. He writes not of love but of lust, of defeats in which nobody loses anything of value, of victories without hope and worst of all without pity or compassion. His griefs grieve on no universal bones, leaving no scars. He writes not of the heart but of the glands.

Until he relearns these things he will write as though he stood among and watched the end of man. I decline to accept the end of man. It is easy enough to say that man is immortal simply because he will endure; that when the last ding-dong of doom has clanged and faded from the last worthless rock hanging tideless in the last red and dying evening, that even then there will still be one more sound; that of his puny inexhaustible voice, still talking. I refuse to accept this. I believe that man will not merely endure; he will prevail. He is immortal not because he alone among creatures has an inexhaustible voice, but because he has a soul, a spirit capable of compassion and sacrifice and endurance. The poet's, the writer's, duty is to write about these things. It is his privilege to help man endure by lifting his heart, by reminding him of the courage and honor and hope and pride and compassion and pity and sacrifice which have been the glory of his past. The poet's voice need not merely be the record of man; it can be one of the props, the pillars to help him endure and prevail."†

It is this spirit with which Dr. Strecker lived and worked, and so well exemplified in his life.

† Taken from *The Age of Danger*, edited by Harold F. Harding, Random House, New York, 1952, Chapter "On Accepting the Nobel Award", by William Faulkner, (p. 397).

Memoir of Frank Ardary Craig (1876–1959)*

By JOHN B. FLICK, M.D.

DR. FRANK ARDARY CRAIG, noted authority on tuberculosis, died on March 11, 1959 in the Presbyterian Hospital, at the age of 82.

He was the last of that group of ardent young men who banded together at the start of the century in the dramatic battle against that dread scourge of mankind, then known as consumption.

On February 3, 1903, the pioneering young Phipps Institute, devoted solely to the study, treatment and prevention of tuberculosis, opened its doors. One month later, March, 1903, Frank Craig joined the group working with Dr. Lawrence F. Flick, who with Henry Phipps, Pittsburgh industrialist, founded the institution.

Soon the youthful Craig was making his first arduous trips to White Haven, a fledgling sanatorium opened in 1901, also under the direction of Dr. Flick. It was then operating in a converted barn and two tents in the mountains of central Pennsylvania.

For fifty years, until his retirement in 1954, Dr. Craig dedicated his life to combatting tuberculosis.

He was born in Philadelphia on September 28, 1876, the son of John Fullerton Craig and Susannah Bird Craig. His father came to Philadelphia as a boy from County Antrim in the north of Ireland, and became a successful sugar merchant, importing his sugar from Cuba. Later he functioned as a trustee of the Presbyterian Hospital and of the Princeton Presbyterian Church, both in Philadelphia. Dr. Craig's mother died when he was a small boy. His stepmother was Emma Camp Craig.

Young Craig's early schooling was in public and private schools. He was graduated from Forsythe School for Boys in 1893 and then entered the second year of the two-year course in biology at the University of Pennsylvania, Class of '94. In the fall he matriculated at the Medical School of the University, graduating in 1898 as president of his class.

Internship at St. Christopher's Hospital for Children followed, and for a while Dr. Craig thought of pediatrics as a specialty. But here began the chain of circumstances that led to his lifework tuberculosis.

In 1900 he went to Pennsylvania Hospital to substitute for Dr. R. N. Willson who was leaving one month before his service ended. Craig stayed on. At the close of his internship, Dr. Frederick Packard of the Pennsylvania staff suggested that Frank Craig go to Vienna for six months of study with the idea of becoming his assistant. On his return to Philadelphia he was shocked to find Dr. Packard in the Pennsylvania Hospital as a patient with typhoid fever—to which he later succumbed.

Before his death, however, Dr. Packard asked Dr. J. Allison Scott to give young Craig some work as his assistant at the Philadelphia Polyclinic Hospital.

It was while following this line of work and serving as an assistant in the medical clinic of the Out-Patient Department of the Pennsylvania Hospital that he was attracted by what he called the possibilities of Phipps' "glorious plan." It was the first hospital in this country to be established for the study, treatment and prevention of one disease.

The opening of the Institute was attended by considerable publicity and several of Dr. Craig's friends had already joined the group of young doctors being recruited for the staff. Decision to sign up did not take Frank Craig long. Soon he and his friends, Dr. Joseph Walsh and Dr. William B. Stanton, took offices together at 732 Pine Street within walking distance of the Institute. At the Institute these young men worked completely on their own resources, acting as physician, clerk and even social service worker.

* Read before the College of Physicians of Philadelphia, 2 March 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Besides the hospital work, young Craig was sent on lecture tours throughout the state and into neighboring states. His assignment was to teach the man on the street how to avoid tuberculosis or how to cure it. And Frank Craig was a born teacher.

Concurrently ran the eventful years at White Haven. Nineteen hundred and six saw him making the first of countless trips as visiting physician to the sanatorium in the rugged hills of Luzerne County. In the early days in order to reach the Sanatorium in snowy weather, after leaving the train it was necessary to ride on a rough farm sledge with boards laid across for seats, and no protection from the wind and cold, often 15 below zero.

"When the roads were icy", Dr. Craig recalled, "it was necessary to stay overnight in the local hotel which was situated so close to the railroad track that, when in bed, the sound of the passing train made one instinctively draw up one's feet lest they be run over."

At White Haven his work as founder and first director of the training school for nurses was a highly important achievement. It followed along the lines of the school already established at Phipps. Both schools were greatly needed, for in those days it was difficult to obtain nurses willing to expose themselves to the contagion of tuberculosis. These nurses, both teachers and pupils, were arrested cases with an understanding of the disease, its prevention and treatment. Being cured themselves, they were enthusiastic for the cure of others.

In 1908, Dr. Craig was one of the most active workers in efforts to bring the International Congress on Tuberculosis to the United States and served on several of the committees. Later he was an active member of the XV International Congress on Hygiene and Demography held in Washington.

On May 16, 1911, he established the first open air school in the United States, this in connection with Phipps Institute. The College Settlement at 433 Christian Street provided the roof for the school and fifteen or twenty children from Phipps Clinic who were tuberculosis contacts, became the pupils. The Board of Education provided a teacher and school equipment.

On November 2, 1916, then in his fortieth year, Dr. Craig married Florence Porter Frishmuth. World War I was at hand and soon he was serving as a member of the Examining Board at Fort Dix. Nineteen hundred and twenty and 1921 found him again in the role of examiner, this time as physician in charge of the Survey of Police and Firemen of the City of Philadelphia.

Dr. Craig might have been described as a rather staid, cautious man, impeccable in dress and manner whom some people found difficult to approach. He was humble, kind, ready to serve anyone who needed him and withal possessed a lively sense of humor which was a surprise to many when they came to know him.

On November 13, 1935, he found himself elected president and medical director of White Haven. He wrote, "It was somewhat disturbing to find myself suddenly transformed from a clinician and teacher to the position of medical director, financier, engineer, dietician, farmer, housekeeper, dairyman, laundry man, chicken farmer, landscape gardener and general pacifier, all fields of experience absolutely new to me."

In 1946, White Haven was transferred to Jefferson Medical College. As far back as 1910 Phipps had become a part of the University of Pennsylvania, but for Frank Craig who had been appointed as Assistant Instructor in Medicine in the University's Medical School in 1903, this was a familiar association. He continued to serve at Phipps in turn as visiting physician, physician in charge of the diagnostic clinic and associate director. In 1932 he became Associate Professor of Clinical Medicine at the Graduate School of Medicine, and in 1942, at the Medical School of the University. He was appointed Professor Emeritus of Clinical Medicine at the University at the time of his retirement in 1954.

Throughout his lifetime Dr. Craig gave generously of his time and knowledge wherever his service was sought. In 1920–21 and again from 1933 to 1947 he served on the visiting

staff of the Tuberculosis Division of the Philadelphia General Hospital and as a member of the Executive Committee of the Medical Board. At the time of his death he was still a Consultant at the Philadelphia General and Presbyterian Hospitals.

He was a member of the Committee on Tuberculosis of the College of Physicians of Philadelphia and of the Philadelphia County Medical Society; past chairman of the Section on Public Health, Preventive and Industrial Medicine of the College of Physicians; corresponding member of the International Union against Tuberculosis and member of President Hoover's Committee on Housing and the Community.

He was one of the founders of the National Tuberculosis Association, first president of the Pennsylvania Trudeau Society and of the William B. Lake Foundation. He was a member of the Executive Committee of the board of the Philadelphia Tuberculosis and Health Association and honorary vice-president of the Pennsylvania Tuberculosis and Health Society of which he was a director for 22 years.

Nineteen hundred and fifty-three was a milestone in Dr. Craig's life. This was the Fiftieth Anniversary of Phipps Institute and he served as chairman in charge of arrangements for the celebration. On Phipps Founders Day he was one of the recipients of a citation by the General Alumni Society of the University of Pennsylvania.

In 1956 occurred another milestone. November 8th was Dr. Craig's eightieth birthday. The Pennsylvania Tuberculosis and Health Society and Phipps Institute joined in celebration. The Board of Directors of the former presented him with an engraved plaque as a testimonial to his unselfish devotion to the battle against tuberculosis and in recognition of his many services in the field of medicine. The Henry Phipps staff presented him with a book of letters, written by friends, students and associates to mark the occasion and testify to the great contribution he had made to the control of tuberculosis, as well as to the personal esteem in which he was held.

In 1958 he received the annual award of the Philadelphia Tuberculosis and Health Association "for a lifetime of outstanding work in tuberculosis control." In May 1959, Dr. Craig was awarded the Will Ross medal of the National Tuberculosis Association posthumously.

Dr. Craig's wife, Florence Porter Craig, died in 1935. There were no children. Dr. Craig had three sisters and five brothers. His sister, Mrs. Herbert Heston, Jr. of Bryn Mawr, is the only surviving member of his family, of his generation.

Dr. Craig lived at 429 Montgomery Avenue, Haverford. He was a member of the Bryn Mawr Presbyterian Church.

Time does not permit listing the numerous other affiliations and the publications where Dr. Craig made contributions in his field. Memorable among his writings were "Early Days at Phipps" and "The Story of White Haven", the only existing intimate records of the two institutions to which he devoted so much of his life.

On June 22, 1959, several months after his death, the old White Haven Bell was shipped to a Presbyterian Mission in Korea, in accordance with Dr. Craig's wishes. For years the bell had hung near the converted barn where the sanatorium had its beginnings. It was rung to call the ambulatory patients to their milk and egg diet noonday meal and to have their temperatures taken. The gift to the Korean Mission was made as a memorial to Dr. Robert Charr, a young Korean who was patient, resident and finally physician at White Haven.

Perhaps the finest tribute of all to Dr. Craig came when in 1954 he was awarded the Medal of the National Tuberculosis Association. It was inscribed, "In honor of the people who for 50 years have carried forward with faith, wisdom and courage the Crusade against Tuberculosis—Frank Ardary Craig."

Memoir of Edward Welles Bixby, Sr. (1887–1959)*

By T. GRIER MILLER, M.D.

EDWARD WELLES BIXBY, SR., elected a Non-Resident Fellow of our College in 1949, was born in Wilkes-Barre, Pennsylvania, on August 3, 1886, and died at his nearby summer home in Glen Summit on August 21, 1959. He secured an A.B. degree from Princeton University in 1907 and his M.D. degree from the University of Pennsylvania in 1911, graduating second in a class of 153 students. Following an internship at the Pennsylvania Hospital he began practice in his home town. Except for a three year period of military service, from 1916 to 1919, he continued the practice of internal medicine in Wilkes-Barre until his retirement for physical reasons in 1955. He had been president of the staff of the Wilkes-Barre General Hospital, as well as its chief of medicine. He was especially interested in tuberculosis and became the director of the State Tuberculosis Clinic of the Kirby Health Center. Also he was on the staff of the White Haven Sanatorium, a member of the Trudeau Society, inspector of the Wilkes-Barre public schools and state medical inspector for his county. In 1935 he was president of the Lucerne County Medical Society and in 1938 he became a Fellow of the American College of Physicians.

Dr. Bixby's military service was noteworthy. He joined the Medical Officers Reserve Corps in 1914. In August of 1916, soon after his marriage to Helen Lea Miner, he was ordered to the Mexican border where he served, as surgeon, with the 9th Pennsylvania Infantry of the National Guard. Then, following the declaration of war with Germany, he was assigned to the 109th Field Artillery of the 28th Division of the regular Army. With that organization, as a Captain in the Medical Corps, he saw very active duty on the Argonne and other fronts.

As stated in an editorial of a Wilkes-Barre newspaper, Dr. Bixby's roots were deep in the soil of colonial America. Two of his ancestors, Joseph Bixby and Thomas Welles, migrated from England to America in 1637, the former settling in Massachusetts, the latter in Connecticut. His father was Charles Welles Bixby and his mother, Anne B. (Davis) Bixby. He is survived by his wife and four children: Dr. Edward W. Bixby, Jr., of Media and Philadelphia; Mrs. Frederick Dasch, of Schuylkill Haven, Pennsylvania; Mrs. James H. Torrey, of West Hartford, Connecticut, and Mrs. John M. Moore, of West Roxford, Massachusetts.

At the University of Pennsylvania Dr. Bixby was a member of the Delta Psi fraternity. Also he was a member of the Westmoreland and the North Mountain Clubs of Wilkes-Barre and of the St. Anthony's Club of New York. He was a Presbyterian.

Dr. Bixby was a charming person, a superb family physician and an outstanding citizen of his community. He was a retiring, kindly gentleman, a gracious host and deeply devoted to his family and many friends. He concerned himself about the emotional as well as the physical problems of his patients and deservedly secured their utmost cooperation and confidence. His services in the Army during the First World War, his activities in behalf of organized medicine and his generous support of, and participation in, efforts to bring about the control and eradication of tuberculosis, together with his personal and professional qualifications, fully justified the high esteem in which he was held by the citizens of his community and by all who knew him.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of Frederick Fraley (1876–1959)*

By JESSE T. NICHOLSON, M.D.

To have met Dr. Frederick Fraley was to become his friend. He was so sincere and conveyed such interest and charm through his manner and speech that all types of people, no matter what their occupation or social state, were his friends. He loved children. They flocked about him and much to his delight, when it was possible, they climbed all over him. Dr. Fraley was born April 12, 1876, in Philadelphia, and he died there on June 25, 1959. His parents were Joseph C. Fraley, an attorney, and Marie Bradford Fraley, who was brought up in Paris where her parents resided. Dr. Fraley attended the Episcopal Academy, from which he graduated in 1892. Throughout his entire life, he maintained a tremendous interest and loyalty to the Academy. He served as school physician for a number of years, and in later years he continued to attend, as a loyal alumnus, the Episcopal football games.

At the University of Pennsylvania, he was a member of the Zeta Psi Fraternity. He received his A.B. degree in 1896, and entered Medical School—to graduate in 1899. While he was awaiting his starting date as intern at the Pennsylvania Hospital, he served a short term as intern at Blockley.

Dr. Fraley's attachment to children gave him an interest in Pediatrics. He was on the staff of the Children's Hospital for many years and served as President of the Pediatric Society of Philadelphia, 1925–1926. He was elected a Fellow of the College of Physicians of Philadelphia on January 3, 1906.

After his marriage in June 1907, to the Former Mary Lapsley Pyle, he maintained an office in his home at 1701 Delancey Place. In the summer, he had a busy general practice at his residence in Northeast Harbor, Maine. There, he made his calls by bicycle until 1920, when automobiles were allowed on Mt. Desert Island. He delighted in giving his children, Josephine and Frederick Jr., rides on the special wooden seat he had fitted on the handlebars of his bicycle.

During World War I, he was a Captain in the Medical Corps and served until March, 1919 at a hospital in Vichy, France. After his return from France, he and his family moved to "Norwynden" in Overbrook. He then shared an office with the late Dr. Arthur Newlin, a classmate at medical school, whose office was at 1804 Pine Street.

Dr. Fraley served for many years on the Board of the Children's Aid Society. From 1926 to 1936, he was Chairman of the Committee in charge of the Nurses' Directory, which at that time was run by the College of Physicians. For many years, he was one of the Managers of the Western Saving Fund Society which, by tradition, has always had one physician on its board.

His outside interests were many and varied. He loved most forms of sports and, while never a great athlete, he played well enough to take great pleasure from sports. He was a cricketer in the days when that game was much played around Philadelphia. He was a devoted tennis player and continued the game until his seventies. At one time, he won the Men's Singles Tournament at the Northeast Harbor Tennis Club, and later was the Chairman of the Tennis Committee. Golf was another favored relaxation and he enjoyed tremendously working to perfect the accuracy of his approach shots and his putting. He delighted in walking and nature study. He was particularly interested in trees, and could identify them by their bark.

Two indoor games which he played well were bridge and chess. He could loose himself in either game and be perfectly oblivious to what was going on around him. He was instru-

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

mental in helping to organize and encourage chess clubs at the Episcopal Academy, at the Western Saving Fund Society, and at the International Students' House.

He was fond of literature, both prose and poetry, and was an avid reader. He was for many years a member of the Shakespeare Society of Philadelphia where he became the Society's "expert" on medical terms and allusions in Shakespeare's plays. He also loved the poetry of Geoffrey Chaucer which inspired him to write much poetry himself in the clear, simply-expressed terms which he admired in Chaucer. An example of his poetry which follows shows another of his enthusiasms, salt water sailing; as well as the philosophical turn of mind which was so much a part of his nature:

THE MORNING WATCH

Wide waste of waters, dim receding stars,
The breeze of dawn that barely fills the sail,
The rhythmic flow of ocean's heaving pulse,
The vagrant seaweed slipping past the rail,
Creak of the rigging, gently furrowed wave,
Under the bows that answer to the swell,
Set sails, wet deck, breath of the salty air,
And clear resounding stroke of brazen bell.
"Our little life is rounded with a sleep,"
Strangers and sojourners we are with Thee.
But we who sail the reaches of the deep
Feel of its might, know its serenity,
Look for the sun in measured course to keep
Appointment with the Morning Watch at sea.

TRANSACTIONS & STUDIES
of the
College of Physicians of Philadelphia

Volume 28
(Fourth Series)

Number 2
(October 1960)

The Etiology of Human Liver Cancer in Africa and the United States of America[1]

By PAUL E. STEINER, Ph.D., M.D.[2]

I DEEPLY appreciate the honor of being invited to give the Thomas Dent Mütter lecture in its 95th year and in this series of distinguished speakers. My satisfaction is especially keen in being able to follow my revered teacher, H. Gideon Wells, who in 1932 spoke on certain advances in cancer. My subject is also on cancer, but of a type that had not yet been described at the time of Doctor Mütter's death in 1859, and about which it was still impossible to speak in etiological terms when Wells lectured here in 1932. Morgagni, in 1769 (1), and Frerichs, in 1862 (2), illustrated tumors in the liver in their atlases but they could not then distinguish between primary and metastatic tumors. One of the first, if not actually the first, microscopically confirmed cases of hepatocellular carcinoma was reported by Weigert in 1876 (3). Although many good descriptions of the histopathology followed, it was not until comparatively recently that the pressure created by the more frequent use of open and needle biopsy and the accumulation of sizeable series of cases resulted in the definitive characterizations of this tumor by Edmundson (4, 5), Ninard (6), and others (7, 8, 9, 10). Today the correct diagnosis is no longer made by exclusion but on positive bases. With this advance came the possibility of doing statistical work of a more reliable type.

Today also it is possible to begin to speak in terms of etiological agents. Three etiological varieties of human liver cancer have been recognized. The thorotrast tumors may be peculiar angiomatous or endotheliomatous growths, but they are further stigmatized by microscopically visible deposits of the agent which is demonstrable also chemically (11, 12). The arsenical liver cancers also may have the unusual morphology shown by the thorotrast tumors, and the excess arsenic, suspected from the clinical history of exposure, is demonstrated by chemical methods (13). The tumors induced by the liver flukes *Clonorchis sinensis* (14) and *Opisthorchis felinus* (15) may be ordinary hepatocellular carcinomas, but they are stigmatized by the presence of the worm and a special pericholangiolar epithelial hyperplasia. These three agents account for only a small fraction of the estimated 2,000 liver cancers in this country each year (16). The causes of the remainder remain to be determined, and they enter into our thinking tonight.

[1] Thomas Dent Mütter Lecture LXXII, College of Physicians of Philadelphia, 3 February 1960.

[2] Institute for Cancer Research, Fox Chase, Philadelphia 11, and Department of Pathology, School of Medicine, University of Pennsylvania.

In parallel developments during the same period of time, liver tumors became inducible in laboratory animals almost at will by physical, chemical, and biological carcinogens. Today, this is the only tumor known to be caused in man and inducible in the laboratory by at least one representative of each of the three large general classes of carcinogenic agents. In addition, it is known in the laboratory that the background of the substratum, namely of the cells on which the carcinogens act, is important. A corresponding factor in man has not been demonstrated for this tumor but it is suspected from geographical and ethnic observations.

Liver cancer is not a major tumor problem in this country. It ranks about twentieth and it comprises only about one per cent of our tumors (16). However, the cytological simplicity of the liver and its response to a great variety of agents have caused it to be widely used to study the histogenesis of cancer. Furthermore, it is the largest colony of epithelial cells in the body. On a comparative basis an epithelial cell in the liver has only a small probability of converting to cancer and then multiplying to a tumor compared with cells in some other locations as, for example, in the uterine cervix. Conversion is a rare event. A comparison of the human liver tumors in an area in which the frequency is low with other regions in which the risk is much higher has, therefore, a considerable appeal.

It became apparent some years ago that primary liver cancer was exceptionally frequent in some parts of the world compared with Europe and America (17, 18). In some areas, this was reported to be the commonest tumor. Almost without exception, the areas reporting high frequencies had poorly developed vital statistics, so that the incidence rates, the true measure of risk, were not known. Recently two rate studies in Africa provided figures of about ten or fifteen times the American figure (19, 20). The areas with high frequency were all either tropical or semi-tropical, or they were in the Orient. Invariably they concerned the Mongoloid or Negroid peoples of the world, but not all such peoples were involved.

The interpretation at first was that the cause was racial, possibly genetical. This was based on such indirect evidence as that the native Javanese had far more liver cancer than did the Chinese or Dutch immigrants living in Java (21), and that the African Native had more than the European resident in Africa (17). Doubt was thrown on the validity of this interpretation when it was reported that the American Negro had the low frequency of the white in the United States and not the high African figure (22, 23). This reduction in a tumor following migration seemed to indicate that environmental factors were important in causation.

At international conferences on liver diseases held in Africa in 1956 (24) and 1957 (25), the various etiological factors considered by the investigators from Africa included malnutrition, African siderosis, toxic native brews and drinks, malaria, schistosomiasis, and viral hepatitis (see 26 for references). There was no agreement on the relative frequency of liver cancer and of cirrhosis in the various parts of trans-Saharan Africa, or on the types and causes of the cirrhosis. Opinion was expressed that liver cancer in Africa occurred only in cirrhotic livers. If this is true, the subject of the relationship of the two diseases needed to be reinvestigated, because this situation would be unique to Africa. Many other problems were posed and a restudy of the total picture seemed desirable.

PRESENT AFRICAN STUDIES

In 1957 it became possible for the present writer to compare liver cancer and cirrhosis in the different parts of trans-Saharan Africa and the United States by carefully re-studying the case collections which investigators in Africa generously made available. By the use of elaborate data sheets and transportable photomicrographic equipment it was possible to get reasonably objective and entirely comparable data on a large scale in a nine month period in nine representative case collections.

Two of the collections had for contrast sizeable numbers of Europeans (*i.e.* Caucasoids) in addition to Natives, and one collection had a third ethnic group, namely, the Cape Coloureds. In all, 904 liver cancers, 943 cirrhoses, and about 1,000 livers having other diagnoses such as schistosomiasis, malaria, epidemic jaundice, hepatic necrosis, yellow fever, kwashiorkor, siderosis, hepatic fibrosis, etc. were studied. The cases represented all of the major ethnic subdivisions of the trans-Saharan African Native, geographical areas as much as 4,000 miles apart, a wide variety of diets, and climates ranging from tropical to temperate and from tropical rain forests to semi-arid. Both bush and semi-urbanized people, and tribal and detribalized persons were studied. With respect to alcohol, it was possible to compare Moslems, to whom alcoholic beverages are forbidden, with pagan and Christianized groups. Africa is so enormous and its people and environment so diversified that few generalizations can be made on environment or race.

It would be impossible to present all the data resulting from this study, and it is not necessary because they are being published in detail elsewhere (26). Here we are interested principally in the findings that bear on etiology.

FREQUENCY

From observations on the admitting policies and in the wards of general hospitals, in morgues, and in post mortem records, it was apparent that the frequency of primary liver cancer varied greatly from one part of trans-Saharan Africa to another, but that even the lowest levels were far higher than in the European in Africa or the white and Negro in this country. Dorn provided incidence rates of 4.6 cases per 100,000 population per year for the white and 4.1 for the non-white in the United States (27). The figures for Davies in Uganda (19) and of Higginson and Oettle for the Transvaal (20) are some ten to fifteen times that rate. Although rate data are not available from the other parts of trans-Saharan Africa, I would classify Uganda and the Transvaal as probably "moderate" or "low" frequency areas compared with the high frequency in places such as the Senegal, the Oriental Province of the Belgian Congo, and Mozambique—to which Berman had previously drawn attention (17). In any event liver cancer is a major tumor problem in many areas. In some hospitals it exceeded all other cancers combined, and the word epidemic was heard.

An interesting feature of the African scene is the observation that in some areas primary liver carcinoma is more frequent than cirrhosis. Instead of cancer supervening in about five per cent of cirrhotic livers as in the United States (16), it occurs in about half, besides which many additional cases occur in non-cirrhotic organs. In Africa, as in this country, about one-third of all liver carcinomas occur in non-cirrhotic organs, provided hepatofibrosis, especially of the secondary type, is excluded from the cirrhosis category. This unusual statistical relationship in Africa puts new light on the old cirrhosis:cancer relationship. It appears that in Africa the main increase is in liver cancer and not in cirrhosis, and that the carcinogenic factor produces now one disease, now the other, and now both in quantities that are nearly equal. There is no reason any longer to consider cirrhosis as a way station to cancer or as participating in its initiation.

CLINICAL, GROSS AND MICROSCOPIC PATHOLOGY

Although the frequency of liver cancer in Africa is much higher than in this country, it appeared to be essentially the same disease, although points of difference were recognized. For example, the clinical history often was of short duration—even only a few hours or days. Some of this brevity may be explained by an uncomplaining attitude or resistance to pain on the part of the native, but it was often due to death from rupture of the hepatic tumor through Glisson's capsule with hemorrhage, which is an unusual complication in this country. Virtually nothing is known about the length of the silent period.

The same gross types were seen as elsewhere, namely, massive, nodular, diffuse, cirrhotic, and others.

The average size of the tumorous liver was about 800 grams larger than in this country, despite smaller average body size and normal liver size in many parts of Africa. The significance of this larger size is not known. The tumorous liver averaged about 800 grams larger in persons without cirrhosis than in those with both diseases. This was interpreted to mean that the combination produced death earlier due to summation of their morbid effects.

In Africa, as elsewhere, only about 60 per cent of the tumors had metastasized outside the liver despite extensive tumor venous thrombosis and dissemination within the liver of a type and extent seen so often in no other tumor.

If primary cancers are histologically classified as hepatocellular, cholangiocellular, cholangiolocellular, hepato-cholangioma, and mixed or collision carcinomas, then the overwhelming majority in Africa were hepatocellular carcinomas. The predominance of this type was greater in Africa than in this country, and it is believed that the added cases are chiefly of this variety. No new or unique types were seen in Africa.

Several curious observations emerged from the African experience. It can be said at once that the cause was not apparent as it is in the thorotrast, arsenical, or liver fluke cancers. Although there was much hepatic cirrhosis and fibrosis, in which new connective tissue was added to the liver, the number of sarcomas, of angioendotheliomas, and of Kupffer cell tumors was not increased. The increase was in the carcinomas, yet benign adenomas and hepatomas were as rare in Africa as they are elsewhere. Furthermore, although liver cancer occurred at a far younger average age than here, the increase came after puberty and not before. Neonatal, infantile, and childhood liver cancers were as rare as they are with us. If an etiological factor was transmitted from parent to child, or if an infantile or childhood experience (such as kwashiorkor) was etiologically important, it exerted its effects only after an interval of several or more decades.

THE AFRICAN CIRRHOSIS

In this dilemma, the cirrhosis in Africa was worth a second look, regardless of whether its role was that of a cocarcinogen or of an indication of liver damage by an agent or agents both carcinogenic and cirrhosigenic.

In Africa, a classification of cirrhosis was used identical with one used on some 400 cases of cirrhosis in the United States. According to this scheme, post-necrotic cirrhosis was diagnosed from the microscopical stigmata of previous collapse of anatomical lobules recognized by the juxtaposition in the fibrous scars or septa of three or more sets of the triadal structures of portal tracts (28).

The cirrhosis in the African was predominantly of the post-necrotic or post-collapse type. The livers tended to be small. The fatty types of cirrhosis were unusual and in some areas even rare. Whatever the cause of the cirrhosis and, inferentially, of the liver cancers, it was of a kind that rarely produced a fatty liver. In the European in Africa, in contrast, fatty liver was as common in cirrhosis as it is in the United States, but an accompanying cancer was unusual (26).

CAUSATIVE FACTORS

With these facts and others at hand from nine geographical areas, ethnic groups and environments in Africa, it was possible critically and realistically to reassess the roles of the alleged causative factors.

The African hepatic siderosis could not account for the liver tumors even if it were carcinogenic, a point that is not established, because it was present in only one of the areas studied, and that area (the Transvaal) was one of moderate cancer frequency.

Malaria also could not account for the liver tumors. The frequency of the two diseases by geographical area was not parallel. The

hepatic effects of malaria are relatively mild and concern the reticulo-endothelium rather than the epithelium.

The same doubt was cast on an etiologic role for schistosomiasis. The Senegal, a high liver cancer area, had little schistosomiasis. The hepatic effects of severe schistosomiasis, of which six types were recognizable, did not resemble the common types of cirrhosis that accompanied the cancers. The geography and the pathology of the two diseases is dissimilar in a number of respects.

No evidence was found to suspect toxic native brews or drinks. The livers were not fatty as after many hepatotoxins. Most of the cancer and cirrhosis occurred in men yet the women are said to be heavier users of the brews. The workers on the gold mines in the Transvaal do not use these brews yet they had their expected quota of tumors.

Alcohol could be excluded as the etiological agent for ethnic, geographical and morphological reasons. The Moslems of West Africa, to whom the use of alcohol is forbidden, showed at Dakar what was probably the highest frequency of malignant hepatoma.

The amount of cancer was not related to any one ethnic group or tribe, and both of the large ethnic groups had areas of both high and of moderate frequency. Liver cancer in Africa was not exclusively or even predominantly a disease of the Bantu. In 558 liver cancers in which the tribe was known, 137 different tribes were represented (26).

The possible role of malnutrition was difficult to assess, not from the viewpoint of overt deficiencies, which were unusual or rare in some of the areas, but from the possibility of hidden grades of inadequacies. There is no evidence at this time that the fatty liver of kwashiorkor progresses to cirrhosis and cancer (24) and much that it does not. The liver in the Native with cirrhosis or cancer was rarely fatty, and in the European the common fatty cirrhosis rarely went on to cancer. If infantile or childhood malnutrition led to cancer, it did so only after an interval averaging about four or five decades and that in a nonfatty organ. In adult Natives the autopsy protocols studied in Africa did not record malnutrition as frequently as did the records recently reviewed in Mexicans, among whom hepatic cirrhosis was not especially common. The workers in the gold mines in the Transvaal get a well balanced diet of up to 5000 calories per day if they wish, despite which they have their full quota of liver cancer.

Examples of hepatitis and hepatic necrosis of types compatible with viral hepatitis were seen in every case collection studied in Africa, although they had not all been so recorded. Little has been written about the distribution, severity, and frequency of infectious jaundice in the trans-Saharan parts of the continent. In two places the disease was endemic if not epidemic during my visit. The cirrhosis was most commonly of the post-necrotic, non-fatty type with a lingering active process as indicated by the inflammatory reaction. Of all the possible etiological factors considered, only hepatitis showed a perfect geographical correlation with liver cancer.

If the virus of hepatitis is the liver-damaging agent responsible for the cancers and cirrhosis in Africa, why are the sequellae so much more severe in the African than in the European in Africa or in other people? A difference in the reaction of the two ethnic groups to the same epidemic was recorded in the garrison at Dakar some years ago (29). The only ready explanation is that subclinical levels of malnutrition might have enhanced the hepatic complications in the Native.

The possibility that viral hepatitis might play an important role in the liver cancer picture in the African was previously emphasized by the French workers (8) and by Higginson in South Africa (24). Only scattered cases of liver cancer have been reported to follow hepatitis in other parts of the world (16). In view of the difficulty of proving this diagnosis, perhaps this infrequency is to be expected at this time.

Proof of the contention that a major cause

of the African liver cancer and cirrhosis might be the hepatitis virus must await practical reliable methods for the identification of the virus or its effects. The same statement can be made about these diseases in the United States and elsewhere. There are people who suspect that the virus is more important in the causation of cirrhosis in this country than was formerly believed. The dividing lines between the different types of cirrhosis are arbitrary, at least in the end stages, and not defensible on a proved etiological basis. Further progress is dependent on a test for virus to a large extent.

One other possible etiological factor emerged from this study. This was altitude. The three areas that appeared to have the highest cancer frequencies lie at low altitudes. Altitude is related to climate and thus to other factors such as diet and disease vectors. This factor, then, might be related to either malnutrition or to viral hepatitis.

My concept of the pathogenesis of liver cancer has been clarified over that previously published (16) by this recent experience in Africa. Knowing now that cancer is more common than cirrhosis in some areas, it becomes reasonable to view both as sometimes caused by the same liver-damaging agent either separately or together. With this concept it is possible to re-orient laboratory investigations.

Thus it is seen that the cause of the great bulk of the cases of primary liver cancer is not yet known, either in Africa or in this country. However, the trail can now be more clearly seen even if the goal is not in sight. Eventually, it is hoped, some of the methods and knowledge gained in this tumor may prove helpful in other varieties of human cancer.

Acknowledgments: The studies in Africa here reported were made on material generously made available by Prof. J. N. P. Davies (Kampala, Uganda), Dr. Charles Berman, Dr. John Higginson and Prof. B. J. P. Becker (all of Johannesburg), Prof. J. G. Thomson (Cape Town), Dr. Gh. Courtois (Stanleyville), Dr. A. Thys (Leopoldville), Dr. D. A. Cannon (Lagos), and Drs. R. Camain and J. Netik (Dakar). Without their cooperation and help this study could not have been made. Study in the United States was aided by a research grant (C3251) from the National Cancer Institute.

REFERENCES

1. Morgagni, J. B., The Seats and Causes of Diseases, Investigated by Anatomy. (Translated from Latin by B. Alexander.) London: A. Millar. 1769. In five books.
2. Frerichs, F. T., Atlas of Pathological Anatomy; Illustrative of a Clinical Treatise on Diseases of the Liver, Pt. 1; II. (Translated from German and ed. by C. Murchison.) London: Williams and Norgate, 1861; 1862.
3. Weigert, C., Onkologische Beiträge. II. Ueber primäres Lebercarcinom. Virchows Arch. f. path. Anat., **67:** 492–522, 1876.
4. Edmondson, H. A., Tumors of the Liver and Intrahepatic Bile Ducts. Atlas of Tumor Pathology, Section VII—Fascicle 25. Washington: Armed Forces Institute of Pathology.
5. Edmondson, H. A., and Steiner, P. E.: Primary Carcinoma of the Liver: A Study of 100 Cases among 48,900 Necropsies. Cancer, **7:** 462–503, 1954.
6. Ninard, B., Tumeurs du Foie; texte; atlas. Paris: E. Le Francois, 1950.
7. Higginson, J. Primary Carcinoma of the Liver in Africa. Brit. J. Canc., **10:** 609–622, 1956.
8. Payet, M., Camain, R., and Pene, P.: Le Cancer Primitif du Foie; Etude Critique a propos de 240 Cas. Rev. internat. hepat., **6:** 1–86, 1956.
9. Steiner, P. E., Cancer of the Liver. Chapter 9 in "Modern Trends in Pathology", edited by D. H. Collins. New York: Paul B. Hoeber, Inc., 1959.
10. Köhn, K., Der Primäre Leberkrebs. Berlin: Springer, 1955.
11. Grampa, G., and Tommasini, D. A.: Hemangioendothelioma of the Liver Following Intravenous Injection of Thorotrast. Acta genet., **8:** 65–78, 1958.
12. Morgan, A. D., Jayne, W. H. W., and Marrack, D.: Primary Liver Cell Carcinoma Twenty-four Years After Intravenous Injection of Thorotrast. J. Clin. Path., **11:** 7–18, 1958.
13. Jhaveri, S. S.: A Case of Cirrhosis and Primary Carcinoma of the Liver in Chronic Industrial Arsenical Intoxication. Brit. J. Industrial Med., **16:** 248, 1959.
14. Hou, P. C.: The Relationship Between Primary Carcinomas of the Liver and Infestation with *Clonorchis sinensis*. J. Path. and Bact., **72:** 239–246, 1956.
15. Kraft, I. (Incidence and Characteristics of Primary Cancer of the Liver in Tobolsk). Vopr.

Onkol., **4:** 321–324, 1958. (Abstr. Excerpta Medica, Sect. XVI (Cancer), **7:** 5, 1959).

16. Steiner, P. E.: Carcinoma of the Liver in the United States. Acta Unio Internat. Contra Cancrum, **13:** 628–645, 1957.
17. Berman, C.: Primary Carcinoma of the Liver. London: H. K. Lewis and Co., Ltd., 1951.
18. Steiner, P. E.: Cancer: Race and Geography. Baltimore: Williams and Wilkins Co., 1954.
19. Davies, J. N. P.: Incidence of Primary Liver Carcinoma in Kampala. Acta Unio Internat. Contra Cancrum, **13:** 606–616, 1957.
20. Higginson, J. and Oettle, A. G.: The Incidence of Liver Cancer in South Africa. Acta Unio Internat. Contra Cancrum, **13:** 602–605, 1957.
21. Bonne, C.: Cancer and Human Races. Am. J. Canc., **30:** 435–454, 1937.
22. Kennaway, E. L.: Cancer of the Liver in the Negro in Africa and in America. Canc. Res., **4:** 571–577, 1944.
23. Steiner, P. E.: The Incidence of a Carcinogenic Factor in the Livers of Cancer, Noncancer, Cirrhotic and Negro Patients. Canc. Res., **3:** 385–395, 1943.
24. Symposium on Cancer of the Liver Among African Negroes, Kampala, Uganda, August 1956. Acta Unio Internat. Contra Cancrum, **13:** 513–873, 1957.
25. The Liver and Its Reactions in Africa. The Leech, **27:** Numbers 2, 3, and 4. (Feb.–April), 1958.
26. Steiner, P. E.: Cancer of the Liver and Cirrhosis in Trans-Saharan Africa and the United States of America. Cancer, In press.
27. Dorn, H. F.: Cancer of the Liver, Infectious Hepatitis, and Cirrhosis of the Liver in the United States. Acta Unio Internat. Contra Cancrum, **13:** 573–578, 1957.
28. Steiner, P. E.: Precision in the Classification of Cirrhosis of the Liver. Am. J. Path., **37:** 21–47, 1960,
29. Charmot, G., Camain, R., and Guidicelli, P.: Place de l'Hepatite Epidemique Icterigene dans l'Etiologie des Cirrhoses Tropicales. Bull. de la Soc. de Path. exot., **46:** 847–860, 1953.

A Consideration of the Mechanisms of Resistance to Viral Infection Based on Recent Studies of the Agents of Measles and Poliomyelitis[1]

By JOHN F. ENDERS, PH.D.[2]

INTRODUCTION

THIS is the second occasion upon which I have had the honor to address the College of Physicians of Philadelphia. Sixteen years ago I was privileged to deliver the Benjamin Musser Lecture at a joint meeting of this College and the Philadelphia County Medical Society. To be twice invited to speak before a body so distinguished gives me unusual pleasure and satisfaction. I am most grateful to everyone who was concerned in inviting me here again.

The title of the present lecture, which I fear may appear somewhat heavy and formidable, was chosen primarily because I believe that recent preoccupation with practical problems of vaccination against virus diseases may have left the impression in the minds of many that specific antibodies play the major, if not the only role, in resistance to these infections. This impression, is, of course, quite erroneous, as Lwoff has well emphasized in the Squibb Centennial Lecture delivered a year ago (1).

While antibody is doubtless of major importance in the prevention of clinical illness following re-exposure, it is equally clear that in primary infections the first line of defense depends upon other relatively less specific factors. These factors, operating in the early stages of the disease when antibody has not yet emerged must serve to limit and buffer a process that otherwise would quickly assume the form of a generalized and overwhelming infection. We also know that even when specific antibodies, capable of neutralizing the infectivity of a given virus have developed, the infection, at least in localized and restricted areas of the body, is able to persist,—sometimes indefinitely. Under appropriate conditions such latent infections may blaze up, as in recurrent herpes labialis, giving rise to overt disease.

The existence of non-specific factors in resistance to viruses has long been recognized and numerous attempts to delineate them have been made. Many, however, have so far resisted precise definition. It is, therefore, not surprising that there has sometimes been a tendency to overlook or minimize their significance. Of late, however, experimental observations have been reported that suggest we may soon arrive at a better understanding of at least some of the non-specific mechanisms responsible for resistance to viral infections. In this lecture I shall summarize and discuss two different sets of data that bear upon this fundamental problem.

SUMMARY OF NON-SPECIFIC FACTORS THAT MAY CONDITION RESISTANCE

Introductory to the presentation of these data, it seems desirable to list the more significant factors that on the basis of available experimental and clinical information may condition resistance or susceptibility. For the sake of convenience these factors can be divided into two groups. The first includes those which depend upon intrinsic physiologic and cytologic processes which may oppose or favor the survival, multiplication and pathogenicity of the virus; the second includes factors coming from without that may modify the protective

[1] James M. Anders Lecture XXXIX, College of Physicians of Philadelphia, 2 March 1960.

[2] Chief, Research Division of Infectious Diseases, The Children's Hospital Medical Center, and Professor of Bacteriology and Immunology, Harvard Medical School, Boston 15, Massachusetts.

effect of the intrinsic factors or induce new and abnormal reactions that depress or enhance the activity of the invading agent. To the first class belong age of the host, type of cell exposed to infection; body temperature reaction (pH) of cells and body fluids; hormones and non-specific naturally occurring antiviral principles like properdin. To the second class belong an equally heterogenous group, such as radiation; vitamins or other dietary components; infection with two different viruses leading to interference or enhancement of the activity of one agent by the other; pre-existing or co-incident disease of bacterial or other origin; and finally, non-specific inhibitory substances initiated by viral infection as exemplified by the principle termed interferon, lately discovered by Isaacs and Lindenmann (2).

To review here even a small proportion of the evidence for the role in resistance of these various factors is manifestly impossible. It must suffice to affirm that in certain instances such as body temperature, cell type, age of host and hormonal balance, the evidence for their effectiveness is impressive. With others the data, while suggestive, are not yet sufficient to demonstrate their importance, at least in human disease. But this uncertainty renders this latter group of particular interest to the investigator. It is, therefore, perhaps not surprising that the findings I shall now present are concerned with two of these factors about which as yet very little is known. One of them, the depressive effect of pre-existing disease, has long been recognized, but the underlying mechanisms of the depressive effect are still largely obscure; the other, only lately defined, is the production of non-specific inhibitory substances by tissue cells exposed to virus.

I shall begin with the results of a study of measles virus infection in two small groups of patients with pre-existing chronic disease. Here, as we shall see, the resistance usually exhibited by normal persons to this agent appeared to be strikingly altered. Afterwards I shall summarize the principal facts regarding the nature and mode of action of interferon and describe investigations, carried out by Dr. Monto Ho and Dr. Edward De Maeyer in our laboratory, which show that a substance comparable to interferon emerges in cultures of human cells infected with the viruses of poliomyelitis and measles. As we proceed I shall consider how these data together with analogous results of other workers may possibly contribute to a better comprehension of the determinants of natural resistance.

THE COURSE OF MEASLES VIRUS INFECTION IN CHILDREN WITH CHRONIC DISEASE

The observations on the influence of pre-existing chronic disease on infection with the measles virus were initiated in 1955. A year earlier Dr. Thomas C. Peebles and I (3) employing tissue culture techniques found that this agent could be readily isolated from throat swabbings and blood of measles patients during the early phase of the exanthem. In cultures of human and monkey renal cells inoculated with these materials changes in cell morphology were observed which were distinct from those induced by any of the viruses that we had previously studied. Subsequently we came to recognize these changes as characteristic of the measles agent. They consist of the formation of syncytia or multinuclear giant cells within the otherwise uniform monolayer of epithelial elements. In the nuclei of the giant cells, as well as in the cytoplasm, eosinophilic inclusion bodies are a consistent and prominent feature. These striking cytopathic effects were readily inhibited by specific antibody which appears in the blood during the early convalescent phase of the disease. It was also shown that an antigen is present in the fluid of cultures infected with the virus which fixes complement in the presence of measles antibody. When monkeys were inoculated with the virus grown in culture they developed viremia and rash and eventually antibodies appeared in their blood capable of neutralizing the cytopathogenic effects of the agent *in vitro*. These results not only served to identify the virus isolated as that of measles but provided

convenient and reliable procedures for its isolation and identification.

Using the tissue culture techniques I have just mentioned, Dr. Kevin McCarthy of the University of Liverpool, England, who was then working in our laboratory, succeeded in isolating an agent from the bronchial secretions taken at autopsy of a child dying of Hecht's giant cell pneumonia (4). This agent was subsequently identified as measles virus. Six months earlier the diagnosis of pancreatic fibrosis had been made in this patient. Although there existed the possibility of exposure to measles on admission to the hospital, the child during a subsequent period of nearly a month exhibited no signs of this disease. Giant cell pneumonia of the type found in this case is a rare disease of children first described by Hecht in 1910 and heretofore recognizable only post mortem. Essentially it is an interstitial pneumonitis characterized by the presence of multinuclear giant cells, containing intranuclear and intracytoplasmic inclusion bodies as illustrated in Fig. 1. The effect of virus recovered from the cases of giant cell pneumonia on cultured human amnion cells is shown in Figs. 2 and 3. These effects are the same as those induced by measles virus under these conditions. Until this study was carried out the etiology of giant cell pneumonia had remained undetermined, but Pinkerton many years ago suggested, largely on the basis of the similarity of the giant cells with the Warthin-Finkeldy cells of measles, that these two conditions might be caused by the same agent.

Subsequently our associate, Dr. Anna Mitus, isolated measles virus from the lung tissue of two additional cases of Hecht's giant cell pneumonia (4). The agent was also recovered from the liver tissue of one of these children. Again no signs of measles were noted,

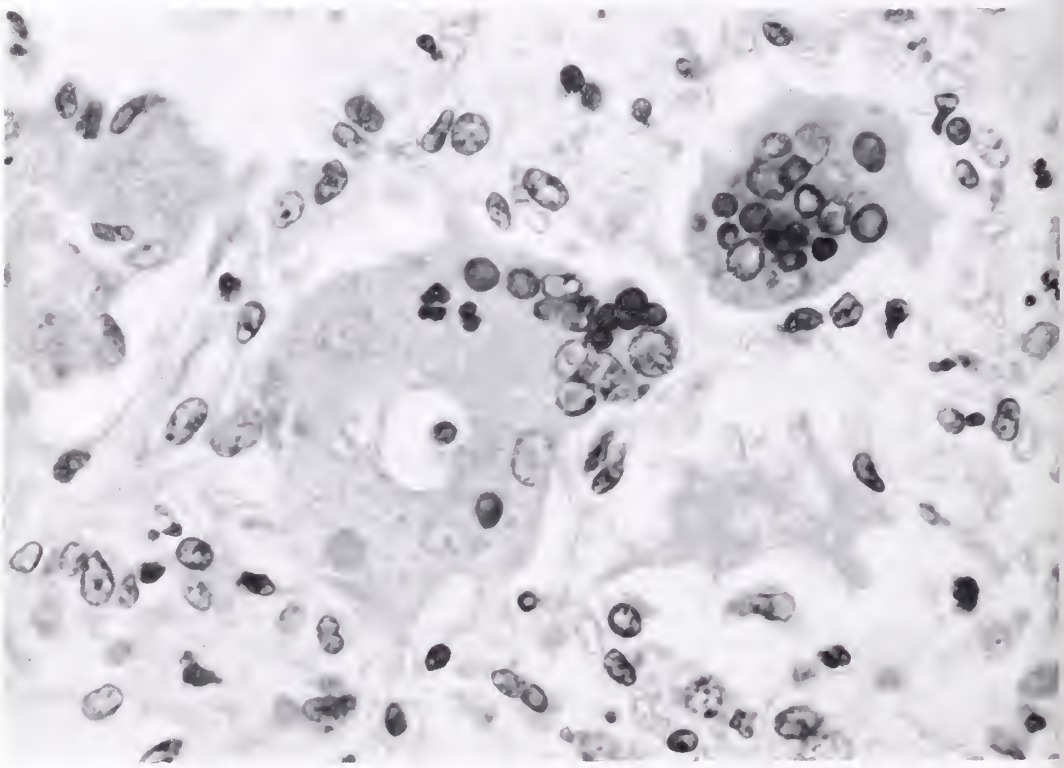


FIG. 1. Section of lung from a case of giant cell pneumonia without rash. H & E stain × 610. (Reproduced by permission of the Editor of the *New England Journal of Medicine* from the article by Enders et al., **261:** 875, 1959).

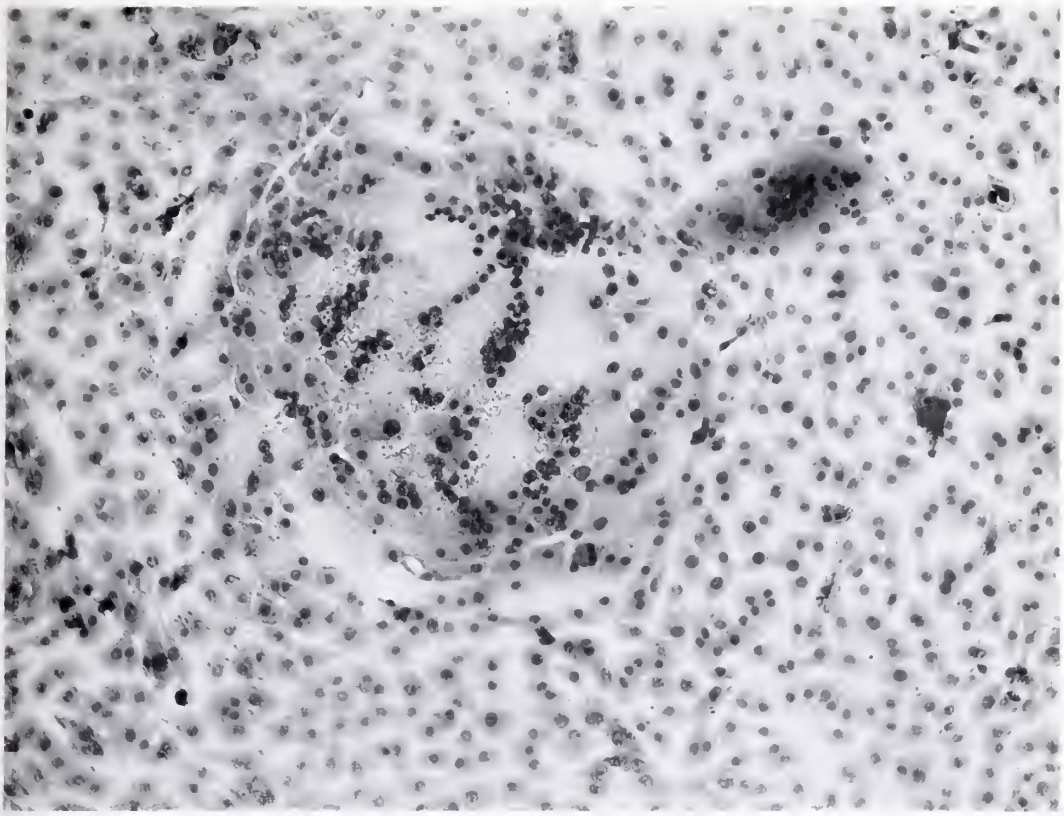


FIG. 2. Syncytium in a monolayer culture of human amnion cells produced by infection with virus recovered from a case of giant cell pneumonia. Normal cells surround the syncytium. H & E stain. × 125.

although exposure to the disease had probably occurred several weeks before death. As in the first case both of these children were suffering from chronic debilitating disease at the time they developed signs of respiratory illness. In one myeloid leukemia had been diagnosed and in the other Letterer-Siwe disease.

Histologic examination of tissues from all three of these cases in addition to establishing the diagnosis of giant cell pneumonia revealed the presence of giant cells or cells with typical inclusion bodies in numerous organs which included, in addition to the lung, stomach, intestines, tongue, bone marrow, lymph nodes, trachea and heart. From these histologic data, together with isolation of virus from the liver of one subject, we may conclude that not only was the virus evidently widely disseminated throughout many different organs, but that it continued to exert its characteristic cytopathogenic effects at these various sites up to the time of death.

Further indications that measles virus infection occasionally runs an extremely abnormal course in patients with leukemia was obtained in a study of four children with this disease who, in contrast to those I have just mentioned, exhibited definite signs of measles following exposure (5). All four children also developed interstitial pneumonitis which in two terminated fatally. At autopsy giant cell pneumonia was identified which proved to be indistinguishable from that observed in the three cases without rash that I have just described. Giant cells were also found in lymph nodes, spleen and bone marrow. Measles virus was isolated from the upper respiratory tract of three of these pa-

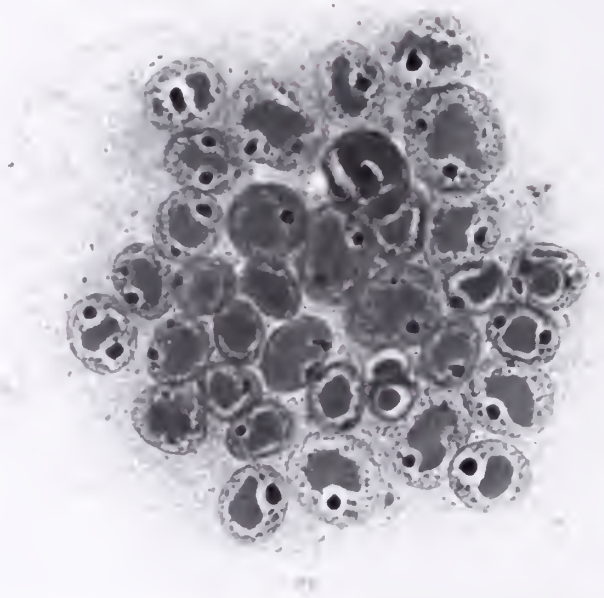


FIG. 3. A group of nuclei in a syncytium produced in human amnion cells by virus recovered from a case of giant cell pneumonia. Note the large eosinophilic inclusions in all nuclei. H & E stain. × 700.

tients, during life and post mortem, from the lungs of two and the liver of one. The relevant data in these 4 cases as well as in the 3 cases of giant cell pneumonia without rash are presented in Table 1.

From the standpoint of the problem of natural resistance, two features of measles as it occurred in these children are of much interest. The first consisted of an unusually long survival of virus in the upper respiratory tract. In otherwise normal subjects the virus quickly disappears from the throat following the appearance of the measles rash. This fact established by workers in the past has recently been confirmed by Ruckle and Rogers (6) and ourselves. In contrast to this usual brief residence of the virus in the upper respiratory tract, the agent was isolated from the 2 fatal cases in the leukemic children 3 and 4 weeks after the appearance of the rash (cf. Table 2). In one of the two patients that survived, the agent was recovered from the throat ten days after prodromal signs of measles was recognized. It seems justifiable to interpret this extraordinary persistence of respiratory tract infection, which in these cases was even more clearly demonstrated than in the children with Hecht's pneumonia, as a reflection of a serious defect in the mechanisms of resistance.

Further evidence favoring this interpretation was obtained from the results of test for complement fixing and virus neutralizing antibodies. Thus in the sera of the two fatal cases taken 3 days before death, that is, several weeks after the exanthem, no complement fixing antibodies could be demonstrated and only traces of neutralizing antibodies were found (cf. Table 2). The presence of the latter could be reasonably attributed to residual gamma globulin which had earlier been administered. Likewise in one of the two patients that recovered no complement fixing and only a trace of neutralizing antibody was detected in the serum obtained one month after the

TABLE 1

SUMMARY OF RELEVANT DATA IN 3 CASES OF GIANT CELL PNEUMONIA WITHOUT RASH AND IN 4 CASES OF POST-MEASLES GIANT CELL PNEUMONIA

NAME	AGE	SEX	Associated Conditions	Meosles Past Hist.	Meosles Exposure	Prophyloctic γ Globulin	Meosles Rosh	Meosles Virus Isolated	Measles Serum Antibodies
D.D.	3	F	Mucoviscidosis	0	+	0	0	Bronch. Secr.	—
C.B.	4	F	Leukemia	0	+	0	0	Lung	—
K.T.	2	F	Letterer-Siwe	0	+	+	0	Lung-Liver	—
J.M.*	3	M	Leukemia	0	+	0	+	Sputum-Lung	Absent
M.C.*	3	F	Leukemio	0	+	0	+	Sputum-Lung Liver	Absent
D.D.	4	F	Leukemio	0	+	+	+	—	Abnormal
R.M.	2	M	Leukemio	0	+	+	+	Sputum	Abnormal

*J.M. and M.C. had measles infection 2 and 3 weeks prior to their bronchopneumonio but did not exhibit typicol meosles rosh during their terminol phose

exanthem. The other child who survived was given a large volume (250 ml) of plasma from a measles-immune donor. Although this rendered it difficult to interpret precisely the serologic tests, the results strongly suggested that here too the antibody response was unusually low.

To appreciate the magnitude of the depression of antibody formation encountered in these children, one must be aware of responses in otherwise normal individuals. Recent studies by Ruckle and Rogers (6), Bech (7) and ourselves (3) have shown that complement-fixing and neutralizing antibodies develop in measles with remarkable speed and regularity and in high concentration. For example, Bech has shown in an examination of sera obtained during a widespread epidemic of measles occurring a few years ago in Iceland that complement-fixing antibodies were detectable in a fairly large proportion of cases as early as 48 hours after appearance of the rash and were present in all cases studied within 3–4 days thereafter. Maximal titers of antibody which ranged between 1:64 and 1:1024 were attained 5–16 days after appearance of the rash.

We now have to inquire why these children with pre-existing chronic disease responded in this bizarre fashion to the measles virus. That their natural defense mechanisms were impaired by drugs employed in the treatment of the chronic condition seems unlikely for the following reasons: none of the patients with leukemia received cortisone or its derivatives during the period of our observations; nor was 6-mercaptopurine administered — a compound shown experimentally in animals to be capable of suppressing antibody formation. All four leukemic patients who were studied serologically were treated with methotrexate, but there is no conclusive evidence to show

TABLE 2

ISOLATION OF VIRUS AND ANTIBODY TITERS IN 5 FATAL CASES OF MEASLES VIRUS PNEUMONIA

Patient	Days after Exposure to Measles or Onset Resp. Dis. Virus Last Isolated	Antibody Titers CF	Antibody Titers Neut
DD*	26	—	—
CB*	29	—	—
KT*	+20	—	—
JM†	±35	<1:2‡	1:4‡
MC†	±46	<1:2‡	1:5‡

* Giant cell pneumonia without rash.
† Giant cell pneumonia following measles.
‡ Serum taken 4 days before virus last isolated.

that this substance affects antibody response. Among the other possible explanations that have occurred to us is a concomitant infection with a second unrecognized agent which might lower resistance to the measles virus just as Dalldorf and Weigand (8) have shown experimentally that simultaneous infection with Coxsackie virus and a non-paralytic poliovirus can result in paralytic disease. No suggestion, however, of the presence of another microorganism was observed. A disorder of the globulin producing mechanism was also envisioned. Again there was no indication of agammaglobulinemia or other disturbance of protein synthesis.

In my opinion the most likely explanation for these aberrant responses seems to be that the efficiency of the factors limiting the infection in normal persons was lowered by the pre-existing chronic disease itself. I should make it clear, however, that one fact stands in the way of accepting this hypothesis without reservation. The course of measles in many children with leukemia and other debilitating diseases does not always follow the pattern we have observed in this small group. Dr. Mitus, for example, has noted a number of cases of leukemia with measles in which the disease presented no unusual features. If, then, we accept the hypothesis that the chronic disease led to the observed depression of resistance in the cases we have just reviewed, we must postulate that it does so only occasionally and under particular circumstances about which it is useless to speculate at present.

From the data I have so far presented, one might jump to the conclusion that the only factor affected in these children was the specific antibody forming apparatus. There are, however indications that the generalized and persistent infection was conditioned by depression of other non-specific factors that may ordinarily limit infection with this virus. Thus gamma globulin given in preventive dosage prior to the onset of measles or signs of pneumonitis apparently failed to check the course of the disease in the leukemic patients. This fact suggests that they were unable to utilize the artificially introduced antibody in the normal manner or that the infection had already proceeded in an unusually rapid fashion to the point where antibody was ineffective. Furthermore it is questionable whether the abnormal persistence of virus in the throat can be attributed to the failure of the antibody-forming mechanism, since the agent was recovered from this site several days after gamma globulin had been administered. Moreover it is doubtful whether the elimination of the virus from the upper respiratory tract even in normally reacting persons is mediated by antibody, since in monkeys, at least, we have shown (9) that infections of the nasopharynx can be established in animals that initially have high concentrations of antibody in the circulating blood.

We have no clue to the nature of the non-specific factors that may have been suppressed in this group of patients. Further light on this basic problem may come through future investigation. One direction that such investigation might take is to determine whether the cells of individuals with leukemia or other debilitating disease are as capable of producing viral inhibitory principles of the sort I am about to describe as are cells derived from normal persons.

Non-Specific Viral Inhibitors—Interferon. Localization of the infective process is characteristic of many different viral diseases. To be convinced of this fact one need only recall the sharply demarcated vesicles of herpes simplex and zoster and other pox diseases, the focal character of the lesions produced by mumps virus in glandular tissue or, in poliomyelitis, the limitation of injury to scattered areas of the spinal cord. Even in viral diseases of the respiratory tract, as in influenza, or those of the brain, as in the viral encephalitides, the damage does not usually extend throughout the entire anatomical system. Until very recently we have been unable to visualize in any definite or satisfactory manner how the infectious process is thus restricted while all about it lies a dense population of unaffected cells, many of which must inevitably be ex-

posed to the virus. The discovery by Isaacs and Lindenmann in 1957 (2) of the viral inhibitory factor which they have named interferon has now enabled us to envision a possible mechanism underlying this puzzling phenomenon of viral localization. The observations of these investigators have already been confirmed and extended by other workers including ourselves.

Interferon was recognized during the course of experiments in which the interfering effect of heat-inactivated influenza virus on viral proliferation was being investigated. Isaacs and Lindenman noted that following exposure of fragments of chick chorioallantoic membrane to the heated virus a substance was produced which was distinct from the virus. It inhibited the growth of the agent used to induce its formation, but what was most surprising and important, it restricted the multiplication of many other related and unrelated viruses. These included Influenza A and B, Newcastle disease virus of fowls, para-influenza virus I, vaccinia and cowpox viruses. The inhibitory effect of interferon could be demonstrated either in chick embryo or in chick cell cultures. Later Ho and Enders (11, 12) and Tyrrell (13) showed that interferons were produced in cell cultures inoculated with active poliovirus type II, measles virus and para-influenza I virus. In Isaacs' hands the activity of interferon was not diminished by addition of antibody specific for the inducing virus. The inducing virus was deposited in the ultracentrifuge at a speed that left interferon in the supernatant fluid. Interferon could also be separated from the inducer by filtration through collodion membranes of appropriate pore size.

Taken as a whole, these results suggest that interferon is not the virus itself or a constituent of the virus. Preliminary studies of its chemical properties indicate that interferon is a protein since it is inactivated by pepsin and trypsin and by shaking with a mixture of amylalcohol and chloroform and is precipitated by saturation with ammonium sulphate. It is resistant to ribonuclease and deoxyribonuclease. There is much experimental evidence to indicate that interferon is a product of cells brought into contact with active or inactive virus under appropriate conditions. It remains for future experiment to determine whether interferon represents an intermediate product of viral synthesis or a normal cell constituent present in very small amounts that is reproduced in excess under stimulus of the virus.

Our own work on interferon-like principles, which I shall now summarize, began quite independently of Isaacs' investigations. It was undertaken with the hope of elucidating the exceptional behavior in cultures of human cells of a strain of Type II poliovirus which Roca-Garcia, Moyer and Cox (14) had previously adapted to chick embryos. This strain has, so far as I am aware, the unique capacity among polioviruses of multiplying in this host. It is also characterized by low virulence for monkeys and for man. When this chick-adapted agent was inoculated into cultures of human kidney epithelial cells no cytopathic changes ensued, although evidence of limited multiplication of the virus was obtained. This lack of cytopathogenicity for human renal cells sharply contrasted with ability of all other strains of poliovirus we have studied to proliferate rapidly and abundantly in this culture system and to bring about profound changes in morphology with final death and disintegration of the entire cell population. In cultures of human amnion cells, however, the chick-adapted agent when introduced in moderate amounts proved to be highly cytopathogenic. To our mind it seemed that this extraordinary difference in cytopathogenicity of the chick-adapted virus for renal epithelial cells on the one hand and amniotic epithelial cells on the other was worthy of further study. Dr. Ho undertook this investigation and soon observed that when undiluted fluids removed from either renal or amnion cell cultures infected with this agent were used to inoculate fresh amnion cell cultures, the cytopathic changes that I have just mentioned did not occur. If, however, such fluids were first diluted and then added to amnion cells, the usual de-

structive effect of the virus was observed. These findings pointed to the presence in the undiluted infected fluids of a factor capable of inhibiting the cytopathogenic effect of the virus. Since it could be readily diluted out of action we concluded that the concentration of this as yet hypothetical factor must be relatively low.

These primary observations initiated a long series of experiments which had the following objectives in view:

a) Determination of whether the observed inhibition in undiluted fluids was caused by substances related to the virus or by a non-viral factor.
b) Determination of whether the inhibitor acted only against the homologous virus or against other agents as well.
c) Determination of some of the physical and chemical properties of the inhibitor.
d) Determination of the mode of action of the inhibitor.
e) Determination of the role of the inhibitor in the maintenance of chronic infection of cell cultures.

I do not propose to describe these experiments in detail since they have already been published. Rather I shall select for brief comment the results which appear particularly relevant to the problem of resistance. Most of the work was done with fluids from cultures of human renal cells that had been inoculated three days previously with the chick-adapted poliovirus; since at about this time the maximum concentration of the inhibitor was found to develop. We have referred to the inhibitor as "viral inhibitory factor" abbreviated as VIF. It was soon demonstrated, just as in Isaacs' experiments, that neutralization of viral infectivity by adding type specific immune serum does not inactivate the inhibitor. The virus could also be separated from the inhibitor by high speed centrifugation. Employing preparations of VIF from which viral infectivity had been removed either by addition of antibody or centrifugation it was found that its activity is rapidly destroyed by treatment with trypsin but not by RNAase or DNAase. It proved to

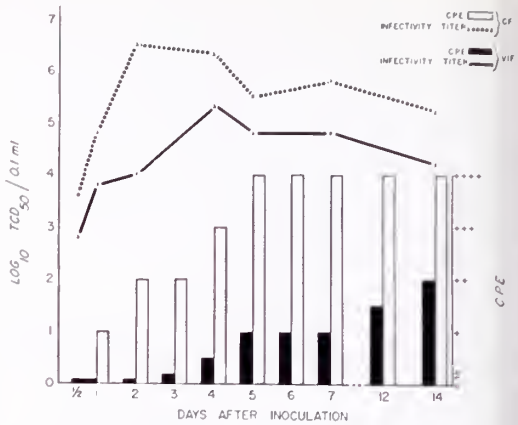


Fig. 4. Effect of viral inhibitory factor (VIF) on growth and cytopathogenic effect (CPE) of Type I poliovirus as compared with cultures treated with control fluid (CF). (Reproduced by permission of the National Academy of Sciences from the article by Ho and Enders, Proc. Nat. Acad. Sci., **45:** 388, 1959.)

be non-dialysable and relatively thermolabile since heating at 56°C for 30–60 minutes resulted in partial loss of inhibitory capacity. These results suggest that the substance is a protein and is closely allied to interferon.

Virus-free VIF was tested for inhibitory effect against the chick-adapted virus poliovirus type II used for its production as well as against a number of other agents which included poliovirus type I and II, vaccinia, ECHO-9, herpes simplex and Sindbis virus. In these tests VIF was added to cultures of human amnion cells and, after incubation for 3 hours at 37°C, moderate doses (100–1000 Tissue Culture Infecting Doses) of the virus to be tested were added. The cultures were then observed daily over a period of 2 to 4 weeks. The degree of inhibition afforded by VIF was estimated by the amount of cell destruction as compared with control cultures to which fluid (CF) from uninoculated cultures had been added. Viral multiplication was determined by infectivity titration in amnion cell cultures of portions of the medium removed at frequent intervals. The results of certain of these experiments are presented in Figs. 4 and 5. It is evident from Fig. 4 that the inhibitor markedly depressed the multiplication

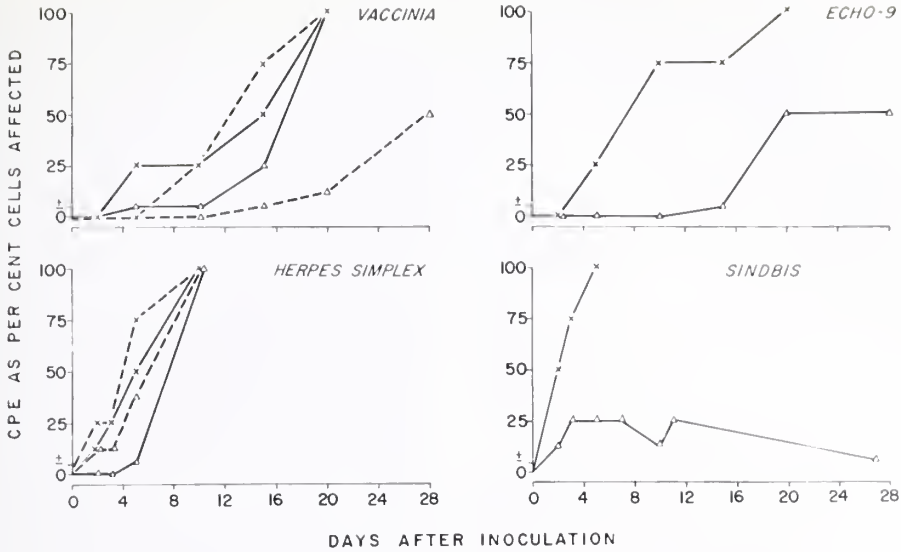


FIG. 5. Effect of VIF on CPE of amnion and kidney cultures infected with different viruses. Amnion and kidney cultures received neutralized VIF and CF and after incubation, 10^2–10^3 TCD_{50} of the different viruses were inoculated. Original fluids replaced 15 days after inoculation with BAF medium. × = cultures with CF; △ = cultures with VIF; — = amnion cultures; ---- = kidney cultures. (Reproduced by permission of Academic Press, Inc. from the article by Ho and Enders, *Virology* **9:** 446, 1959.)

of poliovirus Type I as well as its cytopathogenic effect. Thus, during the course of the experiments 10 to 100 times as much virus was reproduced in control cultures as in those exposed to VIF. Likewise all the cells in control cultures appeared to be injured or dead by the 5th day after inoculation, while in cultures with VIF about one half of the cells were still unaffected at the end of two weeks. From Fig. 5 it will be seen that VIF was about equally efficient in obstructing the cytopathogenicity of vaccinia and ECHO-9 viruses, and exhibited an even greater activity against Sindbis virus. Indeed with Sindbis virus the culture seemed to recover completely from the moderate injury noted at first. Only in the case of herpes simplex was the inhibitor less effective.

Considerable effort was devoted to attempts to define the mechanism whereby this inhibition was brought about. Although a final answer was not forthcoming, it was demonstrated that the inhibitor does not interfere with the adsorption of virus to the cell, which of course, is the first step in the initiation of infection. That viral reproduction is decreased in cells treated with the inhibitor has already been emphasized. This fact was confirmed in repeated experiments using small and large amounts of virus as inocula in which the concentration of extracellular and intracellular virus was measured. It seemed justifiable, therefore, to conclude that the inhibitor in some unknown manner diminishes the intracellular synthesis of virus. But evidence was also obtained suggesting strongly that in addition to the depression of viral synthesis the spread of infection throughout the cell population was retarded in the presence of the inhibitor. This evidence was derived from experiments in which the proportion of infected cells was determined at a time when the cytopathic effects were still minimal. Simultaneously the concentration of virus in the extracellular fluid was also measured. In one experiment in which a strong preparation of VIF was employed it was shown that on the ninth day only 2% of the cells were infected. Yet at this time the fluid surrounding the cell population contained about 3,000,000

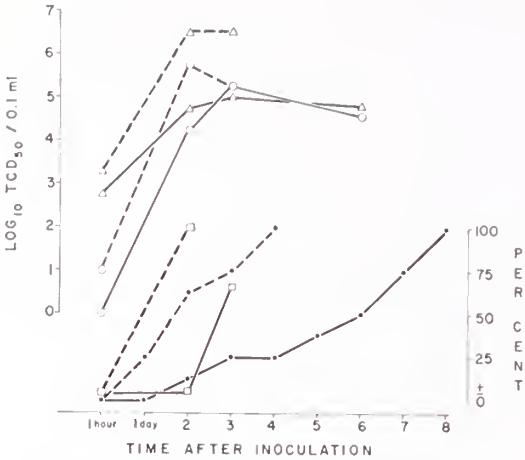


FIG. 6. Dynamics of virus reproduction in amnion cultures exposed to VIF and CF infected with Type I poliovirus. —— = cultures with VIF; - - = cultures with CF; △ = extracellular virus; ○ = intracellular virus; ● = CPE as per cent cells affected; □ = proportion of cells infected per culture in per cent.

infective units of virus or about 50 units per cell! When smaller amounts of inhibitor or very large amounts of virus were added a greater proportion of the cells became more rapidly infected. Nevertheless, the extention of infection was still definitely slower as compared with control cultures (cf. Fig. 6).

In view of these findings, it is not unreasonable to think that the inhibitor, if it is generated within infected areas of the living animal body, might serve to limit the spread of the virus in the same manner as it does *in vitro*.

The recognition of this class of inhibitors has provided a long-sought clue to the mechanism underlying the maintenance of chronic viral infection in cell cultures—a truly fascinating phenomenon observed many years ago by Carrel (15), Feller, Enders and Weller (16) and others. Feller and his co-workers found that when cultures were infected under appropriate conditions, the majority of the cell population presented no signs of injury but continued to metabolize and even multiply coincident with steady proliferation of the virus. This balance between virus and cell survival and growth continued for several weeks or months, when the experiments were terminated. Chronic infections *in vitro* have in the past few years been subjected to intensive investigation by Henle and his associates (17), by Chambers (18), Doherty (19) and others. Among other interesting facts it was shown that the cells in such cultures are not only resistant to the homologous virus but are also resistant to infection with other unrelated agents.

Following the identification of VIF the thought naturally occurred to us that the production of the same factor in chronically infected cultures might serve to explain this intriguing mystery of how a potentially cytopathogenic agent and its host cells can exist indefinitely in a state resembling symbiosis. Accordingly cultures of HeLa carcinoma cells were inoculated with the chick-adapted type II poliovirus (12). The cells were little affected by the virus and continued to multiply throughout a period of eighteen months. During this entire interval the presence of the virus was frequently demonstrated at intervals in low concentration. Assays of the proportion of infected cells indicated that not more than 1% were infected at any one time. Culture fluids removed at various times from the chronically infected cells were assayed for VIF which was found in significant concentrations. These assays were carried out in human kidney cell cultures using Type I poliovirus. However, when cultures of non-infected HeLa cells were used as the test system no inhibition of viral activity was observed. This discrepancy makes it impossible at present to affirm that the inhibitor was an essential factor in the maintenance of the chronic infection. It would seem, however, that this is a likely possibility since Henle and his coworkers (20) have lately described the production of interferon in cultures of another line of chronically infected cells. The interferon produced in these cells proved to be active in uninfected cells of the same line. These workers consider that their result strengthens the suggestion that interferon may play a decisive role in the system they studied.

In conclusion I shall bring to your attention an interesting observation that Dr. De Maeyer has made respecting the production of inhibitor

in cell cultures of virulent and attenuated strains of measles virus. For some time in our laboratory we have been interested in a strain of measles that was attenuated in virulence for monkeys by repeated passages in chick embryos. Lately, trials in children have shown that this virus has also lost much of its virulence for man. Accordingly, we are at present exploring the possibility of employing it as a vaccine against measles.

Recalling Dr. Ho's preliminary experiments in which he had found that considerable amounts of viral inhibitor appear in cultures of human cells infected with measles virus, Dr. De Maeyer has compared the amounts of inhibitor induced by a monkey virulent virus with that induced by the attenuated agent. His results indicate, as shown in Table 4, that cultures infected with the attenuated strain consistently produce from 2 to 4 times as much inhibitor as cultures inoculated with the virulent virus. Not only is this difference of practical value as an additional means whereby virus of different virulence can be distinguished, but it suggests the possibility that attenuation of virulence might be correlated with increased capacity to stimulate *in vivo* the production of inhibitor. This is, obviously, in the light of our present ignorance regarding the development of interferon in the body, a bold and probably unwarranted speculation. But I cannot refrain from making it, since knowledge of the properties upon which virulence depends is almost completely lacking and yet this knowledge is so urgently needed.

(Investigations summarized in this lecture were supported by grants from the Office of The Surgeon General, Department of the Army, and from the National Institutes of Health, United States Public Health Service.)

BIBLIOGRAPHY

1. Lwoff, A.: Bacterological Reviews, **23**, 109, 1959.
2. Isaacs, A. and Lindenmann, J.: Proc. Roy. Soc. B. **147**, 258, 1957.
3. Enders, J. F., and Peebles, T. C.: Proc. Soc. Exp. Biol. and Med., **86**, 277, 1954.
4. Enders, J. F., McCarthy, K., Mitus, A. and Cheatham, W. J.: New Eng. J. Med., **261**, 875, 1959.
5. Mitus, A., Enders, J. F., Craig, J. M., and Holloway, A.: New Eng. J. Med., **261**, 882, 1959.
6. Ruckle, G., and Rogers, K. D.: J. Immunol., **78**, 341, 1957.
7. Bech, V.: J. Immunol., **83**, 267, 1959.
8. Dalldorf, G., and Weigand, H.: J. Exp. Med., **108**, 605, 1958.
9. Enders, J. F., in *Perspectives in Virology*, Ed. by Morris Pollard, John Wiley and Sons, Inc., New York, 1959, pp. 103–120.
10. Isaacs, A., and Burke, D. C.: British Med. Bull., **15**, 185, 1959.
11. Ho, M., and Enders, J. F.: Proc. Nat. Acad. Sci., **45**, 385, 1959.
12. Ho, M., and Enders, J. F.: Virology **9**, 446, 1959.
13. Tyrrell, D. A. J.: Nature, **184** (Suppl. 7), 452, 1959.
14. Roca-Garcia, M., Moyer, A. W., and Cox, H. R.: Proc. Soc. Exp. Biol. and Med., **81**, 519, 1952.
15. Carrel, A.: J. Exp. Med., **43**, 647, 1926.
16. Feller, A. E., Enders, J. F., and Weller, T. H.: J. Exp. Med., **72**, 367, 1940.
17. Henle, G., Deinhardt, F., Bergs, V. V., and Henle, W.: J. Exp. Med., **108**, 537, 1958.
18. Chambers, V. C.: Virology, **3**, 62, 1957.
19. Doherty, R. L.: Virology, **6**, 575, 1958.
20. Henle, W., Henle, G., Deinhardt, F., and Bergs, V. V.: J. Exp. Med., **110**, 525, 1959.

The Unicorn in Medical History[1]

By GENEVIEVE MILLER, PH.D.[2]

. . . and he [the Unicorn] was going on, when his eye happened to fall upon Alice: he turned round instantly, and stood for some time looking at her with an air of the deepest disgust.

"What is this?" he said at last.

"This is a child!" Haigha replied eagerly . . . "We only found it to-day. It's as large as life, and twice as natural!"

"I always thought they were fabulous monsters'" said the Unicorn. "Is it alive?"

"It can talk," said Haigha solemnly.

The Unicorn looked dreamily at Alice, and said, "Talk, child."

Alice could not help her lips curling up into a smile as she began: "Do you know, I always thought Unicorns were fabulous monsters, too? I never saw one alive before!"

"Well, now that we *have* seen each other," said the Unicorn, "if you'll believe in me, I'll believe in you. Is that a bargain?"

"Yes, if you like," said Alice.

From *Through the Looking-Glass*, by Lewis Carroll.

IN 1890, two years after she graduated from the Woman's Medical College of Pennsylvania, Dr. Kate Hurd Mead was working at Johns Hopkins and participating in the activities of the Johns Hopkins Hospital Historical Club led by humanist physicians like Drs. William Osler, William H. Welch, and Howard A. Kelly. These men, she wrote, "inspired me to search among the old archives for the story of women's place in the development of medicine." Thus commenced a lifelong activity relating to her special objective, the history of women in medicine.

It is an honor for me to address you here this evening in memory of Dr. Hurd Mead. It seemed to me that perhaps the subject, the unicorn and medicine, might be appropriate for the occasion because of the important role played by women in the capture of the animal whose horn was at a certain period in the past so highly valued in medicine. Although Dr. Hurd Mead has labelled unicorn's horn as "another quack remedy", which is certainly true when modern standards of judgment are applied, I am sure that if she had placed herself within the intellectual frame of reference of someone she admired like St. Hildegard in the Middle Ages, she would have included the unicorn in her history.

Probably most of you have seen the famous Unicorn tapestries at The Cloisters in New York which depict the best-known medieval legend of the unicorn. Executed for Anne of Brittany at the end of the 15th century, the seven panels portray the hunt and capture of the graceful white creature with the single spiralled horn, the creature which had come, during the Middle Ages, to symbolize Christ. The swift wild creature whose horn was an antidote to all poisons could only be tamed and captured by a lovely maiden in whose lap he docilely laid his head. The maiden represented the Virgin Mary in church allegory, but

[1] Kate Hurd Mead Class of 1888 Lecture in History of Medicine (XII), Woman's Medical College of Pennsylvania. College of Physicians of Philadelphia. Section on Medical History, 19 April 1960.

[2] Assistant Professor of Medical History, Western Reserve University School of Medicine and Research Associate to the Cleveland Medical Library, Cleveland 6, Ohio.

these tapestries undoubtedly represent courtly love as well, since they were probably made to celebrate Anne's marriage to Louis XII in 1499.[1]

The first tapestry shows the beginning of the hunt. In the upper right corner a signal is being given that the unicorn has been sighted. The cipher of Anne occurs five times in the multi-flowered background. At least eighty-five of the more than one hundred plants in these tapestries can be identified by botanists. In the second tapestry the unicorn is seen kneeling beside a fountain and dipping his horn in the waters in order to purify them so that the other animals may drink. The huntsmen stealthily surround the spot, and the third tapestry shows the attack on the unicorn who tried to flee from the huntsmen's spears. A fierce battle follows in the fourth tapestry. The unicorn kicks and pierces a dog with his horn. Unfortunately, only parts have survived of the fifth tapestry which portrays the capture by the maiden. The fragment here shows the smiling subdued beast with a maiden's hand on his neck, while her attendant motions to the huntsman that the hunt is over. In the sixth tapestry the savage attack of the spearmen and dogs on the poor seduced animal occurs. He is then conveyed limp and bleeding on a horse's back to the castle. The last tapestry, which together with the first, was executed later than the others and probably for Anne's daughter, shows the wounded unicorn in captivity, symbolizing both the risen Christ and the consummation of marriage, since the golden chain of marriage binds him to a pomegranate tree, a symbol for fertility, while the fenced enclosure in church allegory stands for the Blessed Virgin and the Incarnation. As we shall see, the erotic interpretation of the unicorn and the maiden probably antedated the Christian one.

Where did the unicorn originate? This is a question which has exercised scholars ever since the sixteenth century when doubts of its existence began to be voiced.[2] The earliest literary report is that of Ctesias, a Greek physician from Cnidus on the coast of Asia Minor, who from around 405 to 397 B.C. served as court physician to the Persian King Artaxerxes. He was present at the battle of Cunaxa made memorable by Xenophon and took care of King Artaxerxes when he was wounded by his brother Cyrus. Ctesias wrote books on Persia and India the original texts of which are lost, but summaries were preserved by Photius, a ninth century Patriarch of Constantinople. In the *Indica*, which was based on travellers' tales, one reads:[3]

> 25. "Ctesias says that there exist in India some wild asses as large as horses and even larger; their body is white, their head purple, their eyes a dark blue. This animal has a horn in the middle of its forehead; it is a cubit long; the base of the horn near the forehead is all white for about two inches; the upper part, the tip of the horn, is a vivid shade of red; the intermediate part is black. Those who have drunk from these horns (for they make drinking vessels of them) are not subject, they say, to convulsions or the sacred disease and even poisons cannot harm them provided that either before or after the absorption of poison they have drunk wine, water, or any other beverage from these vessels. . . .

[1] James J. Rorimer, *The Unicorn Tapestries at the Cloisters. A Picture Book*. New York: The Metropolitan Museum of Art, 1955.

[2] See references in Carl Cohn, *Zur literarischen Geschichte des Einhorns*. Berlin, 1896, footnote p. 3 [Wissenschaftliche Beilage zum Jahresbericht der Elften Städtischen Realschule zu Berlin, Ostern 1896].

Bibliographical note: The most extensive study of the unicorn which has ever been made is that of Odell Shepard, *The Lore of the Unicorn*, Boston and New York, 1930, to which I am indebted for much of the material here presented. Humphrey Humphreys, The Horn of the Unicorn, *Antiquity*, Vol. 27, Mar. 1953, 15–19, first printed in the *Annals of the Royal College of Surgeons of England*, Vol. 8, 1951, is based on Shepard's book and adds no new material. Another recent study, noteworthy for its many illustrations, is Jean Boullet, La merveilleuse histoire de la licorne, *Aesculape*, Vol. 42, Dec. 1959, 3–62. I have not been able to consult Willy Ley, *The Lungfish, the Dodo, and the Unicorn; an Excursion into Romantic Zoology*, New York, 1948.

[3] Ctésias, *La Perse, l'Inde. Les Sommaires de Photius*, ed. by R. Henry. Brussels, 1947, pp. 80–81.

This animal is faster and stronger than any other. There is no other animal, whether a horse or any thing else, which is able to overtake it. It starts rather slowly, but as the course lengthens, its strength increases marvellously and it runs ever further and faster."

Aristotle, who had criticized Ctesias as an unreliable authority, nevertheless believed that two kinds of one horned animals exist, naming the Indian ass and the oryx, a kind of antelope found in Africa.[4] By the time of Pliny four hundred years later, there were three unicorns, for he added an Indian ox to Aristotle's list.[5] Finally Aelian, the second century contemporary of Galen, wrote a book on animals which became a basic text for fourteen hundred years, and here one finds the following detailed descriptions of the unicorn:[6]

III, 41. "India produces horses with one horn, they say, and the same country fosters asses with a single horn. And from these horns they make drinking-vessels, and if anyone puts a deadly poison in them and a man drinks, the plot will do him no harm. For it seems that the horn both of the horse and of the ass is an antidote to the poison.

IV, 52. "I have learned that in India are born Wild Asses as big as horses. All their body is white except for the head, which approaches purple, while their eyes give off a dark blue colour. They have a horn on their forehead as much as a cubit and a half long; the lower part of the horn is white, the upper part is crimson, while the middle is jet-black. From these variegated horns, I am told, the Indians drink, but not all, only the most eminent Indians, and round them at intervals they lay rings of gold, as though they were decorating the beautiful arm of a statue with bracelets. And they say that a man who has drunk from this horn knows not, and is free from, incurable diseases: he will never be seized with convulsions nor with the sacred sickness, as it is called, nor be destroyed by poisons. Moreover if he has previously drunk some deadly stuff, he vomits it up and is restored to health. . . .

And these animals are far swifter than any ass or even than any horse or any deer. They begin to run, it is true, at a gentle pace, but gradually gather strength until to pursue them is, in the language of poetry, to chase the unattainable. . . .

Now the strength of these horns is such that nothing can withstand their blows, but everything gives way and snaps or, it may be, is shattered and rendered useless. They have in the past even struck at the ribs of a horse, ripped it open, and disembowelled it. For that reason the horsemen dread coming to close quarters with them, since the penalty for so doing is a most lamentable death, and both they and their horses are killed. They can kick fearfully too. Moreover their bite goes so deep that they tear away everything that they have grasped. A full-grown Ass one would never capture alive: they are shot with javelins and arrows, and when dead the Indians strip them of their horns, which, as I said, they decorate."

XVI, 20: "They say that there are mountains in the interior regions of India which are inaccessible to men and therefore full of wild beasts. Among these is the unicorn, which they call the 'cartazon.' This animal is as large as a full-grown horse, and it has a mane, tawny hair, feet like those of the elephant, and the tail of a goat. It is exceedingly swift of foot. Between its brows there stands a single black horn, not smooth but with certain natural rings, and tapering to a very sharp point. Of all animals, this one has the most dissonant voice. With beasts of other species that approach it the 'cartazon' is gentle, but it fights with those of its own kind, and not only do the males

[4] *Historia animalium*, Book VIII, 28; Book II, 1; *De partibus animalium*, Book III, 2.

[5] *Historia naturalis*, Book VIII, 30–31; Book XI, 45.

[6] Aelian, *On the Characteristics of Animals*, Trans. by A. F. Scholfield, Loeb Classical Library, Cambridge, Mass., 1958. Permission to quote Book III, 41 and Book IV, 52 has generously been given by the publisher. The translation of Book XVI, 20 is taken from Shepard, *op. cit.*, p. 36.

FIG. 1. The Tibetan antelope, *Pantholops hodgsoni*. From Sven Hedin, *Central Asia and Tibet*, Vol. II, p. 255, and *My Life as an Explorer*, p. 305.

fight naturally among themselves but they contend even against the females and push the contest to the death. The animal has great strength of body, and it is armed besides with an unconquerable horn. It seeks out the most deserted places and wanders there alone. In the season of rut it grows gentle towards the chosen female and they pasture side by side, but when this time is over he becomes wild again and wanders alone. They say that the young ones are sometimes taken to the king to be exhibited in contests on days of festival, because of their strength, but no one remembers the capture of a single specimen of mature age."

Now, we may ask, what were the one-horned animals which these ancient authors were describing? It is obvious that Aelian's "cartazon" of the last passage was a rhinoceros, and that it was a different animal from the wild white Indian ass with the tri-colored magic horn which he had discussed earlier. Aelian does not mention it, but belief in the antidotal power of rhinoceros horn was a very ancient one in India, and Indian potentates had cups and beakers made from its substance, in order to protect themselves from illness. Continuing until modern times, this belief has brought the Indian rhinoceros nearly to the point of extinction.[7]

But what of Ctesias' and Aelian's unicorn with the long horn which was the prototype of the unicorn in the Cloister tapestries? There scholars can only guess. Like the abominable snow man, the unicorn may have originated in Tibet where the natives have long attributed magical powers to a small, fleet antelope, *Pantholops hodgsoni*, whose nearly straight horns are about two feet long. Seen in profile and at a distance by hunters, one might imagine that there were single horned animals in the herd. (Fig. 1) The horns of the orongo, as this antelope was called by the Tibetans,

[7] Lee M. Talbot, Marco Polo's Unicorn, *Natural History*, Vol. 68, Dec. 1959, 558–65.

were carried away by pilgrims because of their magic value.[8]

Another fact which may have led western visitors to the belief in one-horned animals was the Babylonian-Assyrian artistic convention of representing animals in profile with only one horn showing. For example, at the royal palace at Persepolis in Persia there is a sculptured silhouette of a one-horned ox which Ctesias probably was familiar with, an art form which had been going on for over a thousand years, as single horned animals were frequently represented on ancient Mesopotamian cylinder seals.[9]

And how does one explain the tri-colored horn of the unicorn described by Ctesias and repeated by Aelian? One scholar has conjectured that the magical rhinoceros horns may have been artificially dyed after they were taken from the animal. In their natural state they are a reddish black in their thick portion and a dull red where they are thin. The white may have been a further decoration once they became an article of commerce.[10] Thus Ctesias' unicorn appears to have been a composite of fact and fancy, of Asian travellers' tales about an elusive fleet animal bearing only one horn, and with the magic properties of the rhinoceros horn engrafted on that of the more graceful mountain animal.

There is an additional literary source for the unicorn which was crucial for its importance during the Middle Ages and even later—the Bible. The King James English Version mentions the unicorn seven times, for example:

Numbers xxiii, 22: "God brought them out of Egypt; he hath as it were the strength of a unicorn."

Psalm xcii, 10: "But my horn shalt thou exalt like the horn of a unicorn: I shall be anointed with fresh oil."

Job xxxix, 9–10: "Will the unicorn be willing to serve thee, or abide by thy crib?

"Canst thou bind the unicorn with his band in the furrow? or will he harrow the valleys after thee?

Bible scholars have traced the word unicorn of the King James version to the μογόκερως of the Septuagint, the Greek translation of part of the Old Testament made by the Hellenistic Jews in the Greek-speaking community of Alexandria. They employed this word for the Hebrew word *Re'em*, the name of an animal with which they were unfamiliar. But from the characteristics named, the swiftness, fierceness, and the strength of its horn, they judged that *Re'em* must refer to a μογόκερως or unicorn with which they were familiar from Ctesias. Today it is thought that *Re'em* actually referred to a huge aurochs, a species of wild ox, *Bos primigenius*, which is now extinct but was fairly common in the ancient world and is regarded by some as the ancestor of our domestic cattle. Described by Julius Caesar as inhabiting the Hercynian Forest in Germany, they were depicted on Mesopotamian monuments, and the famous sculptured bulls of Nineveh have been identified as aurochs.[11] Incidentally, none of the Biblical passages refer specifically to one horn, and in most instances the pleural was used in the original Greek.

There is still another ancient source for the lore of the medieval unicorn in the *Physiologus*, a group of animal tales assembled in the third century for the purpose of moral edification of the rapidly growing Christian communities. It is well known that objective, scientific descriptions of nature, whether of plants, or animals, or the heavenly bodies, were ignored by the Church Fathers and others who formulated the new Christian religion, and if the natural world was discussed at all, it was for didactic reasons only. Originating in Alexandria, the crossroads between the eastern and western worlds, the *Physiologus* or *Bestiary*, as it was also called in later centuries, was a hodge-

[8] Reports of Latter, Huc, and Prejevalsky, quoted in Shepard, pp. 210–11.

[9] See Eb. Schrader, Die Vorstellung vom μογόκερως und ihr Ursprung. *Sitzungsbericht d. kgl. preuss. Akad. zu Berlin*, 1892, pp. 573–81, Plate 5.

[10] Theory of Shepard, pp. 28–29.

[11] Sir A. H. Layard, *Ninevah and Its Remains*. New York, 1849, Vol. II, pp. 326–27.

podge of stories about animals which served as allegories for instruction in Christian morality. The scientific value of the collection is illustrated by the story of the ant-lion:[12]

"Physiologus says that the ant-lion's father has the shape of a lion and his mother that of an ant. His father feeds on flesh and his mother on herbs. These two bring forth the ant-lion, which is a mixture of both, for his fore part is that of a lion and his hind part that of an ant. Being thus composed, he can eat neither flesh like his father nor herbs like his mother, and so he starves to death."

It is from this source that the story of the maiden's ability to capture the unicorn originates. Although the numerous manuscripts vary in details, in general the animal is described as a small, graceful, kid-like creature which becomes fascinated by a lovely maiden, places his head in her lap, is captured and led away to the palace of the king. In later centuries there were many embellishments to these basic facts, for example St. Hildegard of Bingen in Germany wrote in the twelfth century:[13]

"The unicorn is more warm than cold, but its strength is still greater than its heat. It feeds only on plants and as it walks it nearly jumps. It runs from man as well as from other animals with the exception of those of its own species and for that reason it cannot be caught. It fears man very much and has an aversion to him; just as the snake at the first fall of man turned itself away from man and looked at the woman, so this animal also flees from man but follows women.

"There was once a philosopher who investigated the nature of the animal and he could in no way catch it, which was astonishing. One day he went on a hunt, as he often did, accompanied by women and maidens. This time the maidens separated from the others and played meanwhile with flowers. The unicorn stopped when it saw the maidens, went gently, finally sat on its hind legs and continually gazed at them. When the philosopher saw this, he thought about it and recognized that the unicorn could be caught with the help of the maidens. He approached it from behind and caught it so by means of the maidens. The unicorn, you know, wonders when it sees a maiden from afar, that she has no beard, although she has the form of a man. And when two or three maidens are together, it wonders all the more and becomes all the easier to catch while it has its eye fixed on them. But the maidens with which one wishes to catch it must be aristocratic and not boorish, also not too grown up, but also not too small, but in the true bloom of youth, for this it loves because it recognizes this as gentle and pleasing."

What can be the origin of such a tale? The erotic implications are unmistakable: a beautiful young girl subduing an elusive fleet male beast. (Fig. 2) In the Syriac version of the *Physiologus* the probably pre-Christian origin is even more evident; for the unicorn not only places his head in the maiden's lap but is suckled at her breasts. The text continues: "Then the girl, while sitting quietly, reaches forth her hand and grasps the horn on the animal's brow, and at this point the huntsmen come up and take the beast and go away with him to the king. Likewise the Lord Christ has raised up for us a horn of salvation in the midst of Jerusalem, in the house of God, by the intercession of the Mother of God, a virgin pure, chaste, full of mercy, immaculate, inviolate."[14]

This is another example of the successful syncretism of paganism and Christian beliefs. An ancient tale of the power of a virgin to subdue a fierce male is used to illustrate the power of the Virgin Mary. The captured unicorn symbolized the Incarnation of Christ, its single horn representing the unity of God the

[12] Quoted in Shepard, p. 46.

[13] St. Hildegard, *Tier- u. Artzeneyenbuch*, trans. by Dr. Alfons Huber. Vienna, n.d., pp. 17–18.

[14] Shepard, p. 49, from a Latin translation of J. P. N. Land, *Anecdota Syrica*. Leyden, 1870, Vol. IV, p. 146.

FIG. 2. The unicorn captured by the maiden. From an Italian manuscript of the 14th century, Royal MS. 973. 12, folio xiii, British Museum, reproduced in Shepard, *Lore of the Unicorn*, Plate II.

Father and the Son, its small size the humility of Christ.

During the Middle Ages the unicorn was a universally accepted member of the animal kingdom. Isidore, Bishop of Seville, in the early seventh century included it in his *Etymologies*, an encyclopaedia of all the sciences which was slavishly copied for centuries, and his account occurs without significant variations in later medieval writers like Bartholomaeus Anglicus and Albertus Magnus.[15] Isidore was a genius in jumbling source material, and in the case of the unicorn he confused it with the rhinoceros described by Aelian, mentioning its great strength, cruelty, and its ability to kill an elephant with its horn. Then, in the next sentence, he added the maiden's ability to capture the beast. Fancy a maiden holding the head of a rhinoceros in her lap! Thus unicorns lived on throughout the Middle Ages, firmly established in many texts, both pagan and Christian, and mentioned in the Bible itself. Of course no one ever saw one, but neither did they see elephants or the dragons in which they firmly believed. Such animals simply lived in remote parts of the world which were rarely visited by men from western Europe.

But what of the unicorn's connection with medicine? First of all, it should be noted that there was not a single reference to the unicorn or its horn in any classical medical author, such as Hippocrates, Galen, or Dioscorides. It entered medical literature only late in the Middle Ages. Although Ctesias and Aelian had described the alexipharmic value of the horn, Isidore did not mention it. St. Hildegard in the twelfth century was the first to associate the unicorn with human ailments, as follows:[16]

"Pulverize the liver of a unicorn, give this

[15] Isidore, *Etymologiarum sive Originum Libri XX*, Lib. XII, 2; Bartholomaeus Anglicus, *De Proprietatibus rerum*, XVIII, 88 [edition of Strassburg, 1485]; Albertus Magnus, *De animalibus*, Book XXII, tract. ii, Cap. 1, 106. He seems clearly to have had the rhinoceros in mind.

[16] St. Hildegard, *op. cit.*, p. 19.

powder in fat prepared with yolk of egg and make a salve, and there will be no leprosy, of whatever nature it might be, which would not be healed, if you often rub it with this salve, except if death overtakes him who has it or God will not heal him. For the liver of this animal has a salutary heat and cleanliness in it and the egg fat is very valuable and esteemed as a salve. The leprosy comes of course oftentimes from the black bile and from the black stagnant blood.

"If you make a girdle from the hide of the unicorn and gird yourself with it, no plague however severe and no fever will harm you. Also if you make shoes from the hide and wear them, you will always have sound feet, sound legs and sound joints, and also will no pestilences harm you while you are wearing them.

"If a man is afraid of being poisoned, he should place the hoof of a unicorn under the plate on which the food is or under the cup which contains his drink, and if there is poison in it, they become boiling hot if they are warm, but if they are cold they will begin to steam and thus will he know that poison is mixed therewith."

Oddly, Hildegard gives the hoof the magic power which had formerly been attributed to the horn, ascribing no virtue to the horn itself.[17]

We do not know the source of Hildegard's information or the literary route which established the unicorn horn in the European materia medica.[18] It seems to have been included among new drugs such as bezoar stone and mummy which were added to the European pharmacopoeias from Arabic sources in the late Middle Ages. This same period is also that in which astrology became linked with medicine.

From the fourteenth century on, there are frequent statements about unicorn's horns in inventories of kings and princes. In 1303 a horn was stolen from the treasury of King Edward I of England; in 1388 the French king paid his goldsmith for decorating his unicorn's horn. In 1468 when King Edward IV of England gave a state dinner for the wedding of his sister to the Duke of Burgundy, the table was set with unicorn horns on each corner.[19] If poisoned food or drink were placed on the table, the horns would begin to sweat. During the Renaissance, which coincided with the great Age of Poisoning when no ruler felt safe without some protection against the poison of his enemies, it became customary to touch all foods served with a piece of horn before it was tasted, a practice which was abolished in the French royal household only by the Revolution in 1789.[20]

Complete horns were very costly and were owned only by churches, kings, or wealthy princes. One of the most famous was that of the monastery of St. Denis near Paris. It was seven feet long and was kept in a dark vault standing with one end in water, the drinking of which produced immediate sweating. Jerome Cardan, the colorful Italian physician and mathematician, a contemporary of Benvenuto Cellini, made a special trip to St. Denis to see this horn and was much impressed.[21] This too disappeared in the French Revolution. St. Mark's cathedral in Venice still owns three horns, two of which have been worn smooth by scraping to obtain the medicinal powder. The most famous English horn was that kept at Windsor by Queen Elizabeth and valued by a German traveller in 1598 at 100,000 pounds.

[17] Shepard states (p. 289) that this was a later interpolation in the manuscript which Migne used for his edition.

[18] Shepard states (p. 121) that Albertus Magnus mentioned the horn's magic virtues, and that Peter of Abano "acquired a firm faith in the alicorn [horn of the unicorn] which he transmitted to many others" in his treatise on poisons, *De venenis* (first printed edition, Mantua, 1473). An examination of the texts cited does not yield this information. There is not a single reference to the medicinal value of unicorn's horn in either of these books, and Peter did not even mention the unicorn in his treatise.

[19] Shepard, p. 110.

[20] Article, "Licorne," *La Grande Encyclopédie*, Vol. 22, p. 200.

[21] *De vita propria*, XXIX, in: *Opera omnia*, Lyons, 1663, Vol. I, p. 18.

Another horn kept in the Tower with the Crown jewels was valued at 40,000 pounds in 1641. In 1574 the captive Mary Queen of Scots, fearing that she would be poisoned, wrote to the French Ambassador for fine unicorn's horn, referring to the powdered form.[22] In the seventeenth century Governor John Winthrop of Connecticut became the custodian of several horns, one of them sent by Governor Endicott.[23]

First used in Western Europe only as a detector of poison in food and drink, the unicorn horn gradually was extended to cure a wide number of ailments. Aelian had written that water made from the horn protected one from incurable diseases, convulsions, and epilepsy. The list was enlarged to include poisonous bites, whether of dogs or scorpions, fever, ulcers, and eventually the plague itself. By the late sixteenth and seventeenth centuries its use was no longer confined to those of high estate, for in its powdered or aqueous form it passed into general use as a panacea. Its great popularity is evidenced by the two unicorns in the coat of arms of the Society of Apothecaries of London, created in 1617, and the common use of the unicorn for apothecary shop signs in both Europe and America. The first apothecary shop to be established in Boston by Silvester Gardiner around 1735 bore the sign of the Unicorn and Mortar, while the earliest known pharmaceutical catalogue published in the British American colonies around 1760 described drugs sold in New York at "the Sign of the Unicorn and Mortar."[24] Of interest, too, is the very extensive use of the unicorn for water-marks on paper. Of all animals this was most frequently used, and Briquet's classical catalogue of water-marks lists 535 different unicorn figures in paper from many parts of Europe.[25]

Unicorn horn was listed in official pharmacopoeias such as that of the College of Physicians of London which was first issued in 1618.[26] Here it was included as one of many ingredients of Aqua Bezoartica Langii and of "a great antidote of Mathiolus against poison and the plague," although hartshorn could be substituted if necessary. A London quack's advertisement dating from this same time extolled "A Most Excellent Drink made with a true *Unicorn's Horn*, which doth Effectually Cure these Diseases: viz. Scurvy, Old Ulcers, Dropsie, Running Gout, Consumptions, Distillations, Coughs, Palpitation of the Heart, Fainting Fits, Convulsions, Kings Evil, Rickets in Children, Melancholly or Sadness, The Green Sickness, Obstructions, And all Distempers proceeding from a Cold Cause. The Use of it is so profitable, that it prevents Diseases and Infection by fortifying the Noble Parts, and powerfully expels what is an Enemy to Nature, preserving the Vigour, Youth, and a good Complexion to Old Age: The Virtue is of such force, as to resist an Injury from an unsound Bedfellow; None can excel this, for it is joyned with the Virtue of a true *Unicorn's Horn*, through which the Drink passeth, and being impregnated therewith, it doth wonderfully Corroborate and Cure, drinking it warm at any time of the Day, about a quarter of a Pint at a time, the oftner the better, the Price is 2 *s*. the Quart."[27]

By this time we must all be asking the question: where did these horns come from? Travellers as recently as the nineteenth century claimed to have seen unicorns of various descriptions in remote parts of the world, in Asia, central Africa, or even America, but none

[22] M. H. Armstrong Davison, The Maladies of Mary Queen of Scots and Her Husbands, *Scottish Society of the History of Medicine, Report of Proceedings*, 1955–56, p. 32.

[23] *Mass. Hist. Coll.*, Ser. III, Vol. X, p. 20; Ser. IV, Vol. VII, p. 156.

[24] Henry R. Viets, The medical education of James Lloyd in Colonial America, *Yale J. Biol. Med.*, Vol. 31, 1958, 5; facsimile of titlepage of pharmaceutical catalogue in *Am. J. Pharm.*, Vol. 131, 1959, 19. My attention was brought to the latter by Dr. Fred B. Rogers.

[25] C. M. Briquet, *Les Filigranes, Dictionnaire Historique des Marques du Papier*, Paris, 1907, Vol. III, pp. 519–36, Nos. 9922–10457.

[26] *Pharmacopoea Londinensis*, London, 1618, pp. 4 and 74.

[27] From a collection of tracts assembled by Anthony à Wood, preserved in the Bodleian Library at Oxford, reproduced as Plate XI in Shepard.

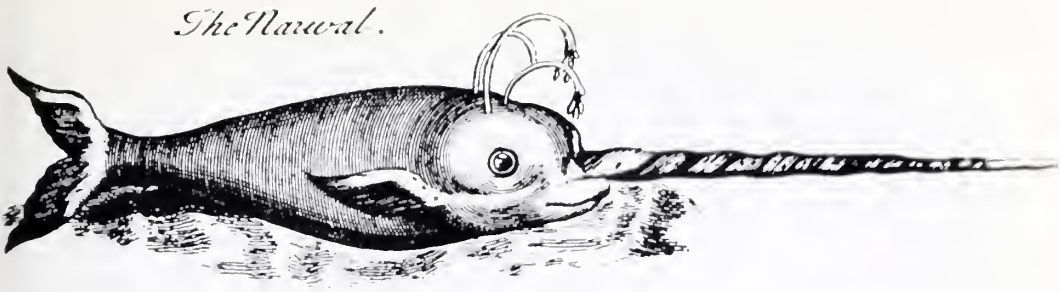


FIG. 3. The narwhal, *Monodon monoceros*. From Pomet, *Compleat History of Drugs*, London, 1725, Plate 81.

were ever seen in Europe. What was the source of supply of this drug which eventually became rather plentiful, either whole or in powdered form? The most famous horns were long, slender and spiralled like the one in the tapestries. From what animal were they obtained? The answer is that they were not obtained fron any land animal at all, but from a mammel of the sea, the narwhal, *Monodon monoceros* which inhabits waters of the far north and is rarely seen south of Greenland. The male grows from ten to eighteen feet in length and bears a single long tusk on the left side of its upper jaw which may extend for more than half the length of the animal. (Fig. 3). It is not a horn, but an ivory tooth with a central cavity and with spiral grooves and ridges on the surface.[28] The first "horns" were probably found on beaches where they had washed up from the sea, like the famous "Horn of Windsor" found by Frobisher in 1577 in the Baffin Island bay which bears his name. As one of his men reported, they saw "a dead fish floating, which had in his nose a horne streight and torquet, of length two yards lacking two ynches, being broken in the top, where we might perceive it hollow, into the which some of our sailers putting spiders they presently died."[29]

From the thirteenth century on the steadily increasing activities of Scandinavian seamen in the waters around Iceland and Greenland brought an ever greater number of "unicorn horns" to markets in Amsterdam and Copenhagen whence merchants distributed them all over Europe. Also in the sixteenth and seventeenth centuries the Portuguese brought rhinoceros horns from India, for their contact with the Indians whose faith in the power of rhinoceros horns was ages old served to amplify the popular belief in unicorn horns. Of course there were disputes about which of these horns were "true" unicorn horns, especially since one was black and the other white, but authorities for both types could be cited. More important was the necessity to avoid buying false horns, for the market was such a good one that many substitutes were proferred. Artificially straightened walrus or elephant tusks, fossil bones, or stalactites were sold as true horns, and the powdered form could be made from innumerable substitutes such as powdered bones of any kind, stag horns, or even clay.[30] Therefore it was necessary to have tests to determine whether or not the horn

[28] Article "Narwhal," *Encyclopaedia Britannica*, Eleventh Edition, Vol. XIX, p. 243.

[29] Dionise Settle, *The second voyage of Master Martin Frobisher, made to the West and Northwest Regions, in the yeere 1577, in:* Richard Hakluyt, *The Principal Navigation Voyages Traffiques & Discoveries of the English Nation*, Vol. VII, New York, 1904, p. 219. See also the account of George Best: "Upon another small Iland here was also found a great dead fish, which as it should seeme, had bene embayed with yce, and was in proportion round like to a Porpose, being about twelve foote long, and in bignesse answerable, having a horne of two yardes long growing out of the snoute or nostrels. This horne is wreathed and straite, like in fashion to a Taper made of waxe, and may truely be thought to be the sea Unicorne. This horne is to be seene and reserved as a Jewell by the Queenes Majesties commandement, in her Wardrope of Robes." *Ibid.*, p. 297.

[30] Thomas Browne, *Pseudodoxia epidemica: or, enquiries into very many received tenents, and commonly presumed truths*, London, 1646, pp. 167–68.

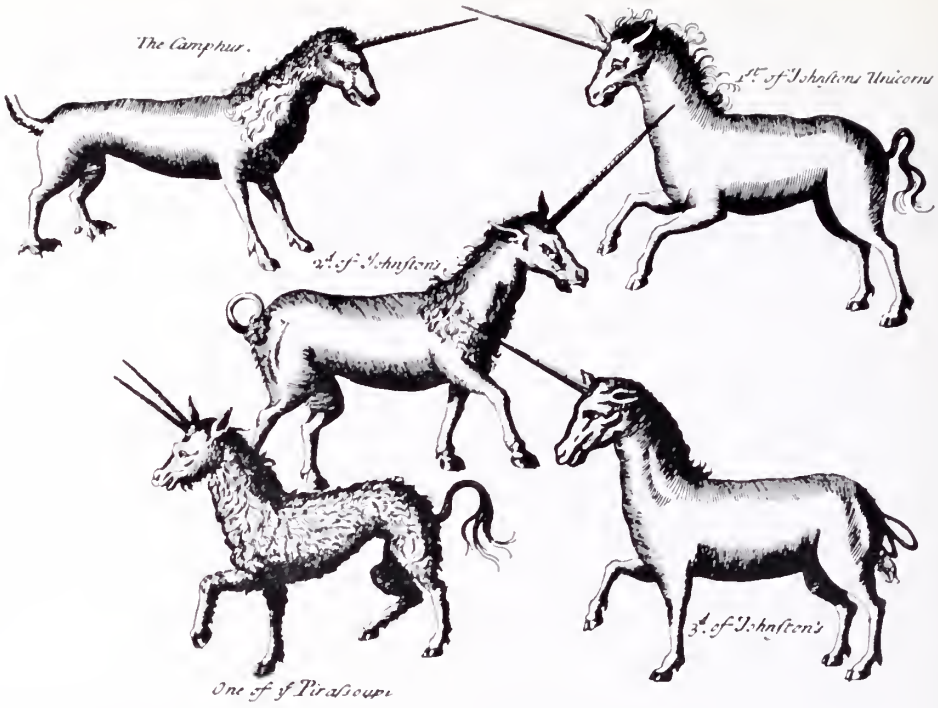


Fig. 4. Various kinds of unicorns. From Pomet, *Compleat History of Drugs*, London, 1725, Plate 70.

was genuine. Frobisher's sailors dropped spiders inside their horn to see whether or not they would die. True horn when put into water would cause bubbles to rise and the water would appear to boil even though cold; moreover live scorpions put into such water would die after a few hours. Or if one traced a circle with unicorn water and placed a scorpion, spider, or toad within this circle, it would die when it crawled over the edge.[31] In another test a pigeon which had previously been poisoned with arsenic could be revived by feeding it powdered unicorn horn.

A public exposure of the traffic in narwhal tusks took place in Copenhagen in 1638 when Professor Ole Worm, an anatomist of repute, presented a dissertation in Latin about the unicorn horns which the local merchants were selling, a dissertation, oddly enough, prepared at the request of the merchants themselves, who had become engaged in a dispute about what these horns really were.[32] Professor Worm described the most famous horns of Europe and showed that they were all identical with narwhal tusks. He had personally examined a narwhal cranium and had seen that the tooth or tusk protuded from the left side of the upper jaw and not from the cranium, as a horn should. In spite of this dissertation, which few probably read anyway, confidence in the medicinal value of unicorn horn did not wane. Instead people simply transferred to the tusk of the narwhal, or sea-unicorn as it was called, the virtues which the terrestrial unicorn horn had had, and one writer praised God for providing from the sea such an abundant supply of a product which had formerly been so rare and costly that only princes could afford it.[33] As one might expect, the increased

[31] Ambroise Paré, *Des Venins et morsure de chiens enragez . . .* Chap. LXI, in: *Oeuvres*, Lyon, 1641, p. 519.

[32] *An os illud quod vulgo pro cornu Monocerotis venditatur, verum sit Unicornu.* The text is given in Thomas Bartholin, *De Unicornu Observationes*, Amsterdam, 1678, pp. 113–18.

[33] Paul Ludwig Sachs, *Monocerologia, seu de Genuinis Unicornibus*, 1676, quoted in Shepard, pp. 263–64.

supply brought the value of horns down considerably by the middle of the seventeenth century, but this does not signify that public interest or confidence was slackening. One of the chief sights of European travellers in this period was the famous throne made almost entirely from unicorn horns which was used for the coronation of the Danish kings.[34]

However there were also sceptics who had been speaking out for some time. "Great account and much profit is made of Unicornes horne," wrote Sir Thomas Browne in 1646, "at least of that which beareth the name thereof; wherein notwithstanding many I perceive suspect an Imposture, and some conceive there is no such animall extant."[35] Browne was referring to a controversy about the unicorn which had begun in the middle of the preceding century. Conrad Gesner had included a detailed account based upon traditional sources in his *Historia animalium* of 1551, but two years later Pierre Belon, the French naturalist who had travelled in parts of the world where the unicorn was supposed to live, was sceptical about the animal and the presumed powers of its horn. He judged that most of the European horns were from marine animals, an area of knowledge in which he was a competent judge.[36]

In 1566 an Italian physician named Andrea Marini wrote a book "Against the False Opinion of the Unicorn"[37] which thoroughly criticized the belief that such an animal as the unicorn existed and that any of the so-called unicorn horns had any medicinal value whatever. He blamed the Arabs for having introduced many false drugs, such as unicorn horn or bezoar stone, and he branded such usages as based upon groundless superstitions, human credulity and gullibility. In addition to using a method of comparing texts in order to demonstrate the innumerable contradictions in the descriptions of the supposed animal, (Fig. 4) Marini performed experiments with the horn itself, as did the great French surgeon, Ambroise Paré, shortly afterwards. Paré's "Discourse on the Unicorn" of 1682 reinforced all of Marini's arguments.[38] It is interesting to note that Paré's religious faith prevented him from denying that unicorn animals exist, since they were named in the Holy Scriptures, but as there was no mention in the Bible of any alexipharmical virtue of the horn, Paré was free to disprove this with all possible experiments and logic.

Both Marini and Paré provoked response by unicornists, as we may call them, whose arguments demonstrate the resourcefulness of the mind in providing arguments for wishful thoughts. One author, for example, insisted that the reason that the unicorn is never seen is because it is so rare, and being so rare it is all the more valuable.[39] An opponent of Paré appealed to the weight of time and authority for belief in the unicorn. It must exist because for centuries so many people and so many famous authors had said so. This brought forth Paré's famous statement that he "would prefer to be right entirely alone than to be wrong not only with the wise men but even with all the rest of the world. For the excellence of truth is so great that it surpasses all human wisdom."[40]

Another interesting attitude is observed in those who defended the unicorn: the notion

[34] "But of these *Unicorns* Horns no man sure hath so great a Collection as the King of *Denmark*; and his Father had so many, that he was able to spare about an hundred of them, to build a Magnificent Throne out of *Unicorns* Horns." Edward Browne, *An Account of several travels through a great part of Germany*, London, 1677, p. 20.

[35] Thomas Browne, *Pseudodoxia epidemica*, p. 166.

[36] *Plurimarum singularium & memorabilium rerum in Graecia, Asia, Aegypto, . . . observationes*, Antwerp, 1589, Lib. I, cap. 14 (pp. 35–38). First published in French in 1553.

[37] *Discorso de Andrea Marini, Medico, Contra la Falsa Opinione dell' Alicorno*, Venice, 1566.

[38] *Discours d'Ambroise Paré, Conseiller, et Premier Chirurgien du Roy. A Sçavoir, De la Mumie, De la Licorne, Des Venins, et de la Peste*, Paris, 1582. This treatise was discussed in a recent article by Boyd Howard Hill, Jr., Ambroise Paré: Sawbones or Scientist? *J. Hist. Med.*, Vol. 15, 1960, 52–56.

[39] Andrea Bacci, *Discorso dell'Alicorno*, Florence, 1582, pp. 36–37.

[40] *Réplique d'Ambroise Paré, . . . à la response faicte contre son Discours de la Licorne*, in: *Oeuvres*, p. 522.

FIG. 5. Frontispiece of the second edition of Thomas Bartholin's *De Unicornu Observationes*, Amsterdam, 1678. By courtesy of the National Library of Medicine.

that even though it might be true that the unicorn horn is valueless as a detector or antidote to poison, nevertheless it is good for the state to have people believe in it, since this prevents evil men from committing crimes by poisoning.[41] Paré tried to dissuade the physician of King Charles IX from the ceremony of dipping a piece of horn into the King's drinking

[41] Bacci, *op. cit.*, passage translated by Shepard. p. 167.

cup. The physician replied that he knew that it was a useless custom, but since everyone believed in it so thoroughly he could not stop it. When asked why physicians prescribed powdered unicorn horn to patients when they knew it was worthless, Paré said, "It is because the world wants to be deceived and physicians are very often forced to prescribe it, or rather, to permit their patients to use it because they want it."[42]

The unicorn literature was brought to a suitable climax with the efforts of the three Bartholins, Caspar, Thomas, and Caspar the Younger. The 1628 treatise by Caspar which gave a sober critical examination of the issue was extended by his son Thomas to a volume which is both a serious and a comic encyclopedia on the unicorn. The second edition of this work by Caspar the Younger contains references to nearly six hundred books and practically exhausts the subject of one horned creatures, whether insect, fish, animal or man.[43] (Fig. 5) The general position taken by all the Bartholins was that the unicorn animal does exist in nature, but its horn is valueless in medicine. This remained the commonly accepted belief of educated people. So long as the word unicorn remained unexplained in the Bible, the existence of the animal had to be accepted by the pious, and so long as there were unexplored parts of the world, one could never be sure that the classical unicorn might not some day be found.

Slow as the popular opinion was in changing, it is clear that by the end of the seventeenth century no self-respecting practitioner would prescribe unicorn horn. Quincy's *Dispensatory* of 1722 dismissed the drug as follows: "The strange Conceits of the Medicinal Virtues of this Drug are both too numerous and too ridiculous to mention here; and both this and the following [bone of a stag's heart] are now justly expelled [from] the present Practice."[44]

In the Western Reserve University Library catalogue the cards for "Unicorn" are immediately before those for "Unidentified Flying Objects." Could anything be more suitable, expressing as they both do man's perpetual desire for the miraculous, the unattainable, for freedom from the commonplace, and for the means of escape from illness and death?

[42] *Oeuvres*, p. 520.

[43] *De Unicornu Observationes Novae*, 1645; 2d edition, Amsterdam, 1678.

[44] John Quincy, *A Compleat English Dispensatory*, 4th ed., London, 1722, p. 185.

A Guide to Health—'*An Epistle to a Friend*' (Thomas Jefferson) by Charles Willson Peale[1]

By FRED B. ROGERS, M.D.[2]

MARK TWAIN once stated that the two most popular topics for conversation are health and the weather—and that one could do something about the former! Health is, indeed, like the weather. The better it is, the more we take it for granted, but, unlike the weather, if health is not satisfactory, we can do something about it. Good health, through the ages, moreover, has been appreciated to be more than not being sick. Robust living may be summed up in the word *vitality*. Knowing and applying basic facts about diet, rest, cleanliness, and exercise is important, as well as one's mental outlook on life. Gautama Buddha put it well long ago: "Health is the greatest blessing of all." (Arogya parama laba.)

The subject of personal hygiene—a capstone in preventive medicine—has been a concern of thoughtful people over the centuries. Much advice and numerous testimonials—both lay and professional—have appeared on this subject. Galen's *Hygiene* (c. 180 A.D.), addressed to all people interested in medicine; the *Regimen Sanitatis Salernitanum*, a popular thirteenth-century poetic guide to health; Luigi Cornaro's *Treatises on Sober Life*, published by the noble Venetian in his advanced age (1558–1627); and Johann Peter Frank's *System einer vollständigen medicinischen Polizey* (1779–1827), are historical examples of guides to better living. These particular publications and their authors were recently reviewed by Dr. Henry E. Sigerist in his book, *Landmarks in the History of Hygiene* (1956.)

An early American publication on personal hygiene came from the pen of Charles Willson Peale, an eminent artist somewhat afield in this authorship. His guide to health was written in 1802 and published by Jane, daughter of Robert, Aitken as a 48 page booklet at Philadelphia in the following year. Addressed to an ailing friend (who was President Thomas Jefferson) it presented health rules found valuable by the author during his life—which he said, was "chiefly a series of experiments" in this and other matters. The full title of this unusual item is: *An Epistle to a Friend, on the means of Preserving Health, promoting happiness; and prolonging life of man to its natural period. Being a summary view of inconsiderate and useless habits that derange the system of nature, thereby causing premature old age and death. With some thoughts on the best means of preventing and overcoming disease.*

Its author, Charles Willson Peale (1741–1827), was a native American genius, a man, like his friend Benjamin Franklin, of catholic interests and diverse talents. Best remembered as a portrait painter, he was also a distinguished citizen, soldier, and naturalist. (The College of Physicians of Philadelphia owns two portraits by Charles Willson Peale—those of Dr. Thomas Cooper and Alexander von Humboldt, and three portraits by his son, Rembrandt Peale—of Dr. John Carson, Georges Cuvier and Joseph Gay-Lussac.) Descended from a line of English clergymen, Charles was born on April 15, 1741, in Queen Anne County, Maryland, where his father was then principal of a public school. Early talent in art led to an introduction to John Singleton Copley and tutelage of Benjamin West in London. Outside his calling as an artist, Peale served as an infantry officer at the Battles of Trenton and Princeton during the Revolutionary War and subsequently was

[1] Read before the Section on Medical History, College of Physicians of Philadelphia, 17 November 1959.

[2] Professor of Preventive Medicine, Temple University School of Medicine, Philadelphia 40, Pennsylvania.

elected to the General Assembly of Pennsylvania. Drawings of the bones of a mammoth later transformed his art gallery into a repository of natural curiosities—open for public exhibition. Moved to the American Philosophical Society in 1794, and, in 1802, by Act of the Pennsylvania Assembly into Independence Hall, Peale's "Philadelphia Museum", as it was called, under the direction of a Board of Trustees, was a notable collection of its time. Charles Willson Peale also was largely responsible for the establishment of the Pennsylvania Academy of the Fine Arts in 1805.

Peale was a man with several avocations—interests in applied science and the arts, youthful ventures in trade and a successful politician. He was thrice married; of six children by his first wife, Raphael and Rembrandt became painters, and Titian and Rubens, naturalists. From his second marriage came six children, of which, Franklin and Titian Ramsey were best known as naturalists. Charles Willson Peale died at Philadelphia on February 22, 1827, and was buried in St. Peter's Episcopal Churchyard. He left manuscript journals and memoirs, in addition to published and unpublished writings. These observations covered a wide scope of literary, scientific and philanthropic subjects.

A little known publication is his "Guide to Health", an epistle prompted by the illness of a friend, Thomas Jefferson. Peale often met Jefferson at meetings of the American Philosophical Society, to which the former was elected in 1786, and the latter was longtime president (1797–1815). The *Epistle*, which enjoyed a popular sale at Peale's Museum, contained a good deal of common sense and clear observation on a matter of life-long interest, part of the enlightened eighteenth-century revolt against traditional lore in which Peale wholeheartedly participated. He took a sanguine view of life, however, and his belief that a sensible and natural course would *ipso facto* double or triple the life span has not yet been altogether realized.

For his text, on the title page of this booklet, Peale quoted a contemporary English author, Robert Southey (1774–1843), ("*Inscriptions* § 2" last line): "Reflect that man creates the evil he endures." The *Epistle*, directed from Peale's "MUSEUM", March 3, 1802, was prefaced in part by these remarks, "The following sheets were occasioned on hearing of the indisposition of a person in a public station, whose death would be a public loss. As the latter advanced, the subject became more interesting, and naturally led to reflections that were not necessary to communicate to the person it was intended for, and having other friends to whom the ideas it contained might be acceptable, determined to have it printed, with a greater detail of reflections, under a

AN

EPISTLE

TO A

FRIEND,

ON THE MEANS OF

PRESERVING HEALTH,

PROMOTING HAPPINESS;

AND

PROLONGING THE LIFE OF MAN TO ITS NATURAL PERIOD.

BEING A SUMMARY VIEW OF INCONSIDERATE AND USELESS HABITS THAT DERANGE THE SYSTEM OF NATURE, THEREBY CAUSING PREMATURE OLD AGE AND DEATH, WITH SOME THOUGHTS ON THE BEST MEANS OF PREVENTING AND OVERCOMING DISEASE.

BY CHARLES W. PEALE.

"Reflect
"that man creates the evil he endures."

Philadelphia:
From the Press of the late R. AITKEN,
No. 20, North Third Street.
BY JANE AITKEN.

1803.

FIG. 1. Title page of Peale's *Epistle*. Copy in the Library of the College of Physicians of Philadelphia.

fond hope that by using strong, yet simple language drawn from facts, founded on actual experiments, that it might induce some of my readers to think for themselves, and on consulting their feelings, thus be led to the manly resolution of governing their conduct by reason, and to act independent of fashion or custom.

"The preservation of health is so very important, that we might suppose that no well-disposed person could be led into any kind of excess or intemperance, knowing the natural consequence to be not only debility of the body, but also of the mind. . . . This essay . . . may inform (those) that are disposed to think, and thus do good."

The substance of Peale's rather quaint thesis was that health is paramount to a happy, useful life, and that reasonable men can alter their destiny in health matters. He noted that people usually advocate what pleases them in such concerns. "At an early period I asked Doctor (Alexander) Hamilton senior (1712–1756) (an eminent Physician near Annapolis), what is the best drink for health? 'Toddy mun', the old Gentleman replied in his caledonian dialect . . . The fact was, that the Doctor loved Toddy; in like manner, most people advise what they are most fond of." Peale did not agree with Dr. Hamilton that fermented beverages were the best drinks—he recommended water, a glassful with each meal. Tolerance to liquors, he noted, however, varied with individuals—recalling William Osler's later comment that 'abstinence' permitted "a mint-julep before breakfast south of the Mason-Dixon Line."

The writer next stated that, "Man, who is a rational animal; unless he is governed by his reason, is led by variously excited appetites to an abuse of many of the blessings bestowed on him." He likened his own life to a series of experiments—employing useful comparisons and exclusions to determine habits of health which should not be transgressed. A long life, Peale concluded, would naturally result from care in hygienic matters. He would have agreed with the British Lord Avebury that, "Plain living and high thinking will secure health for most of us."

"It is not a life of privation", Peale wrote, "but rather of every enjoyment, that I contend for; it is only the *abuse* of good things which I condemn." Like Benjamin Franklin, he advised one not to eat to dullness, or drink to elevation. Peale was, in short, a moderate person and his *Epistle* consequently is a warmly human document. He advocated coffee, "as the French take it, after dinner", and chocolate, as tasty, wholesome beverages. Shunning wines; he advocated water as the best table beverage—he mentioned his own endeavors for providing potable water on land and aboard ships, and cited like interests by his sons, Raphael and Rembrandt. The latter he proudly wrote, "while exhibiting the Skeleton of the Mammoth at New York gave demonstrations on obtaining pure water to those engaged in maritime concerns" in that seaport.

Meats he mentioned as a chief nutriment, suggesting thorough cooking, preferably by boiling, with use of the stock, "with fat skimmed off", in soups. Vegetables he recommended in small quantities, preferably steam-cooked according to a method devised by his friend Dr. Robert Patterson, physician—mathematician at the University of Pennsylvania, and the American-born Count Rumford in Europe. Peale deemed pickles, certain nuts, (excluding walnuts) and mushrooms—"the whole class"—as unfit for human consumption. Directions for the preparation and baking of bread, "the staff of life", with a useful recipe, were included for practical use.

The use of tobacco came under strict censure: "a nasty, loathsome, and pernicious custom . . . the evil, productive of personal filth, offensive breaths and dirty habitations." Peale said that tobacco also altered the quantity and quality of saliva, so essential for proper digestion.

As an illustration of the benefits of good regimen, Peale used the homely example of a horse, purchased at auction, "had wind-galls, etc., he foundered with my first ride of only

five miles in an easy gait . . . I determined to be tender of him; and fed him well, but with care, and made very short journeys. By perseverance and good management for a great length of time, restored him—so much was his constitution improved, that when he was an old horse he would travel far, and carry a greater load than most horses I met with."

Posture received attention also—the manner of walking, sitting and lying down. "Man, in his most beautiful form, is like a wedge with the apex downward; the shoulders broad; chest full, and from thence tapering down to the feet. Women on the contrary, are esteemed most handsome, when broadest at the middle; the best form for the purposes of the sex; their thorax rather smaller than in man, that their swelling breasts may not project too much."

Adequate rest—"six or eight hours of repose" for adults, with additional naps, if needed, were prescribed. He noted: "On no account ought we to slumber after the moment of our *first waking in the morning*, should that happen after the early dawn or before the sun has risen."

Reading aloud, he thought, was a service to the lungs—"to throw off peccant matter obstructing the vessels" . . . "*Singing*, is also serviceable, yet needs no recommendation, as it is derived from, or accompanied with a natural impulse of love, and happily never wants advocates."

The importance of mental hygiene, of tolerance and helpfulness, were also alluded to: "Serenity of mind goes a great way to overcome causal disease; the effect of *good actions* amply reward men independent of other duties. The natural ties and dependance we have on each other, should obligate us to have a respect for opinions which may not accord with our ideas, either of religion or politics . . . With such a disposition of mind, and the proper attention to cleanliness and other means of preserving health . . . we need not fear attending on the sick, and fulfilling every tie of duty or gratitude." During the contemporary yellow fever epidemics, in 1793–98, he noted, inhabitants fled from Philadelphia because it became a "fashion." Peale mused, "How wonderfully strange that man will not reason, and act independently, but that he so frequently will be governed by the opinions of others. . . . If this position is true, how very important it is that those, from whom the public take their tone, should be wise, circumspect and prudent, who will adopt the best customs of every country, and embrace the most beneficial means to *promote economy, health and happiness*."

To *Masters of families*, Peale had this to say: "Not only by good examples, but by *love, the youthful mind must be won to acts of virtue and good conduct*, which is much easier, and certainly more agreeable to a tender parent than coercive means. . . . Parents ought to reflect what their feelings were in their youthful days, and not be so rigid as to restrain their children from innocent amusements." Parents, he added, might join their children in occasional "frolicks", such as the theatre or social dancing. Peale was himself a wise and loving parent. "The philosopher", he stated, "is not degraded by sometimes joining in the sports of children." A personal anecdote was supplied to illustrate his sage advice: "A splendid father and equally virtuous and good mother" had a son, Charles, who enjoyed dancing at the Assemblies. The father frowned on this amusement as a waste of time and thought it best not to permit the son such indulgence. "At the end of a certain busy day, the father, retiring to bed, asked if his son had come home yet. Sleeping lightly because of this concern, the father fell off to sleep on hearing bootsteps on the stairs—those of mother wearing father's boots and kicking the steps as she ascended to make her husband believe that his son was hurrying to bed." This "farcical anecdote", Peale qualified, was not the sort of deception that should become routine in a household!

Urging nature study as essential for proper development of children's minds, Peale quoted one of his own lectures on Nature: "The

early education of children must generally fall on the *mother*, how important then, that she should be well informed in the history of *Nature*. What a delightful amusement it must be, to teach her sweet prattlers, as their minds expand, the various changes, from the creeping caterpillar to the dormant chrysalis, and gay fleeting butterfly; and also the various metamorphoses of other insects;—to know their uses in the support of other animals,—that they may be led to abstain from cruelly or wantonly tormenting them. Thus instilling and extending as they advance in years, *a sweet benevolence* of temper toward their brethren. . . . What charming conversations will a knowledge of this science afford between the father and his sons, at the age when they become agreeable and useful companions to each other."

Exercise, taken frequently and in moderation, was considered essential for optimum health. "Sleeping in a tent last Summer, that I might be ready to direct the workmen in getting the bones of the Mammoth from a deep morass, a cold wind arose in the night, which blowing on one of my shoulders, produced a violent rheumatic pain." Massage and a gradual return to work restored the part. "Had I indulged my inclination for rest, I might have been crippled in the arm for months."

Peale suggested that clothing should be loose and supported from the shoulders—to avoid constriction of the waist or extremities. "Overalls" are preferable for heavy work. Flannel is best next to the skin—keeping parts warm but avoiding overheating.

"*Cleanliness* is commendable, besides being condusive to health . . . begin with washing the hands and feet: and after completely cleaning the whole frame, rub till perfectly dry with a *coarse* linen towel. . . . Frequent *bathing* is good through all seasons, but more especially in Summer. . . . A *shower-bath* is recommended by some; but not so safe as the *plunging-bath* which I esteem a great luxury, either cold or warm as circumstances may require." Baths, he noted, also often reduced fever and ameliorated bodily pains on occasion.

"Doctor (Joseph) Priestley (chemist and Unitarian clergyman exiled to America from England in 1794), informed me of a vapour-bath, and the construction of one he used, with which two or three quarts of boiling water made a complete bath. I have invented sundry important improvements on that described by the Doctor, and under the hope of making them of general use, obtained a patent for my improvements."

"A glyster"—or enema—was recommended by Peale for gastrointestinal disorders—suggesting that it be self-administered by means of an "apparatus". In yellow fever and children's colic, especially, he reported flaxseed tea—administered per rectum—of some benefit.

"*Health*", the author urged, "is a blessing that too much pains cannot be taken to obtain, and preserve; and with which every other consideration, when put in competition, is of no account." To his worthy friend, Thomas Jefferson, he concluded this epistle, "That you may enjoy every good gift and abuse none, is the wish of your friend, Charles W. Peale."

We know from correspondence preserved and printed in the Princeton University series, *The Papers of Thomas Jefferson*, that the philosopher-president acknowledged and valued the advice offered by his well-meaning friend. Like Peale, Jefferson was a rational truth-seeker. Each was a lasting ornament to the history of our nation. That each of these great Americans was genuinely concerned about personal hygiene and public health was a valuable aspect of their long and useful lives.

Acknowledgment: The author acknowledges assistance by two descendants of Charles Willson Peale: Augustin R. Peale, M.D., Professor of Pathology, Temple University School of Medicine, and Charles Coleman Sellers, Litt. D., Librarian of Dickinson College, Carlisle, Pennsylvania.

REFERENCES

1. Sellers, Horace Wells: *Charles Willson Peale, April 15, 1741–February 22, 1827;* in *Dictionary of American Biography,* vol. XIV, pp. 344–347, New York, Charles Scribner's Sons, 1934.
2. Bridenbaugh, Carl (editor): *Gentleman's Progress: The Itinerarium of Dr. Alexander Hamilton, 1744,* Chapel Hill, University of North Carolina Press, *1948,* pp. xiii, 202.
3. Sellers, Charles Coleman: *Charles Willson Peale. Later Life (1790–1827),* Philadelphia, Memoirs of the American Philosophical Society, vol. 23, pp. 231, 268, 347, 1947.
4. Boyd, Julian (editor): *The Papers of Thomas Jefferson,* Princeton University Press, 1950 *et seq.*

Memoir of Joseph D. Aronson (1889–1958)*

By ESMOND R. LONG, M.D.

JOSEPH DAVID ARONSON, Professor of Bacteriology at the Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis of the School of Medicine of the University of Pennsylvania, and a member of its staff for nearly forty years, died at Paramaribo, Dutch Guiana on October 17, 1958 while on a field trip in the investigation of leprosy.

Dr. Aronson was born in Lithuania in 1889. He was brought to this country in infancy and acquired American citizenship when his father became naturalized. Attracted at an early age to the study of medicine, he entered the Medico-Chirurgical College of Philadelphia, where he attained his M. D. degree in 1908 at the age of nineteen. He served his internship at the Philadelphia General Hospital, and spent a year as instructor in surgical pathology at the Medico-Chirurgical College. From 1911 to 1914 he was Professor of Pathology and Bacteriology at the University of Arkansas in Little Rock. His faculty positions in these formative years, and courses of study in the summers at the University of Chicago and University of Vienna, proved invaluable training in both teaching and research.

In 1914 he returned to Philadelphia to assume a position in the laboratories of the City Bureau of Health, of which Dr. C. Y. White, a colorful figure in Philadelphia medicine, was Director. For a short time later he was Director of the City Hospital Laboratory in Greenville, South Carolina.

In 1917–19, in the first World War, he served as captain in the American Expeditionary Force in France. In Paris he was assigned to the Pasteur Institute, where he made the acquaintance of leaders in tuberculosis work, and became a particularly close friend of Drs. A. Boquet and L. Nègre. He cherished this friendship all his life, and renewed it in person when he went overseas again in 1944 in the second World War as Commanding Officer of the 361st Medical Laboratory, again at the Pasteur Institute. He was discharged from the Army in 1946 with the rank of colonel, after a fruitful service of several months with the Army Institute of Pathology in Washington, during which he made an exhaustive analysis of fatal tuberculosis in the World War II Army.

In 1920 Aronson became a full time member of the staff of the Henry Phipps Institute. His life henceforth was devoted to medical research. The problems in which he was interested were those of infection, immunity and allergy and the bacteriology of acid-fast microörganisms. He began his studies with investigations of tuberculin and the tuberculin reaction in association with Paul A. Lewis, Director of the Laboratory of the Phipps Institute. His later investigations included studies of methods of tuberculin testing, types of tuberculin, the significance of the reaction, and procedures in mass tuberculin testing. Much of the technique employed today, and the measurements used in evaluating the tuberculin reaction, date back to Aronson's early studies. His first paper, published with Paul Lewis in the American Review of Tuberculosis in January 1923, was the initial report in a long series of investigations that brought Aronson recognition as the country's chief authority on the technique of tuberculin testing and the management of field tests.

His studies included a sustained investigation, from 1931 to 1934 of tuberculous infection, under a cooperative arrangement between

* Read before the College of Physicians of Philadelphia, 6 April 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

the International Health Division of the Rockefeller Foundation and the Phipps Institute. Eugene Opie, who had succeeded Paul Lewis as Director of the Laboratory at the Phipps Institute, had maintained a close association with the Rockefeller Foundation, and was deeply interested in Aronson's studies. These investigations led to well-known papers on the prevalence of infection in different parts of the country. The figures were of much interest then for comparison of rural areas in the North and the South, and of lasting value for comparison with the much lower rates of tuberculous infection disclosed by tuberculin tests today.

Proceeding from tests on animals and human beings, Aronson began tissue culture studies on tuberculin, which are now recognized as pioneer investigations in this field. He was one of the discoverers of the cytotoxic reaction to tuberculin in tissue cultures from tuberculous animals, a field which is yielding results of importance at the present time.

Simultaneously with these studies he was engaged in independent research on tuberculosis in cold blooded animals. He became the American authority in this field. He discovered, isolated, grew in artificial culture, and determined the pathogenicity of acid-fast bacilli in fish, frogs, snakes and other cold blooded animals. His name is attached to some of these organisms in official classifications (e.g., *mycobacterium marinum* (Aronson) from salt water fish and *mycobacterium thamnopheos* (Aronson) from garter snakes). These studies led him to investigations of leprosy, to which he devoted much attention for a considerable period of his life, and in which he was engaged at the time of his death. He was a bacteriologist of unusual skill in the cultivation of acid-fast bacilli.

In the late 1920's he commenced the work for which he is best known, his studies on BCG vaccination. His original interest had been excited in France through association with investigators at the Pasteur Institute. When he returned to Philadelphia he began studies in cooperation with the pediatrician Arthur M. Dannenberg, and in 1935 these two published a pioneer article in the *American Journal of Diseases of Children* on the vaccination of infants and children in Philadelphia. In this paper a favorable influence in protecting against mortality from tuberculosis was reported. In 1935, under arrangements made between the Phipps Institute and the United States Office of Indian Affairs, Aronson initiated statistically controlled field trials of the value of BCG vaccine in North American Indians. These studies were continued for more than twenty years; during this time a continuous series of papers appeared on the prevalence of infection, the tuberculin reaction in vaccinated persons and controls, the waxing and waning of the reaction, and the degree of protection afforded. All of these studies, characteristically, were controlled by Aronson through correlated experimental studies in guinea pigs. He was much concerned at all times with the problem of standardization of tuberculin. He had a wide acquaintance in Pennsylvania and used many state institutions as proving grounds for his epidemiological studies. From 1948 to 1958 he conducted a BCG vaccination program for the Commonwealth of Pennsylvania.

In the course of his studies on tuberculous infection among Indians in the Southwest, the importance of correlated studies on fungus infections in the region became clear to him. In the preceding years some confusion had developed in the diagnosis of tuberculosis in areas where histoplasmosis was prevalent. In the Southwest and West a similar situation had developed in the case of another fungus infection, coccidioidomycosis. Aronson made extensive studies of both of these fungus infections in Arizona and New Mexico, and in Pennsylvania for comparison. These researches added notably to our understanding of the differentiation of these diseases from tuberculosis.

Aronson's final years were spent in keeping his BCG investigations up-to-date, and carrying studies forward on the metabolism and bacteriology of acid-fast organisms other

than tubercle bacilli. With the aid of funds from the United States Public Health Service he embarked upon studies of leprosy in which he returned to the age-old problem of its etiology. He was attempting to isolate the acid-fast bacilli readily seen in leprous tissues in leprosy, but never cultivated to the full satisfaction of any investigator, by inoculating cold blooded animals, hamsters, and other laboratory animals with material from cases of the disease. Because of the recent considerable reduction in the extent of leprosy in regions from which specimens could once be readily supplied, he found it necessary to make field trips to distant regions where specimens could be obtained. Although in failing health—he had shown signs of decompensation of the heart for some years—he undertook difficult travel at great cost to his strength. He and Mrs. Aronson were at work in leprosy institutions in Surinam, Dutch Guinea, when he died suddenly in the midst of his labors. He was buried in the National Cemetery at Arlington with military honors on November 12, 1958.

Dr. Aronson became a Fellow of the College of Physicians of Philadelphia in 1942. In 1947 he was awarded the Alvarenga Prize of the College for his work on BCG vaccination. In 1949 he received the distinguished service award from the Department of the Interior "for his eminent career and outstanding contribution to the public service." He is survived by his wife, Charlotte Ferguson Aronson, and three sons. His unfinished work is being carried on by Mrs. Aronson and other associates.

Dr. Aronson's major objective in life was the discovery of new facts. This search for truth was matched only by his indefatigable industry. He was first, last and always a scientist, and unsparing of his own strength in his devotion to his work. He was a good citizen, steadfast in the principles to which he adhered, intent on public affairs, deeply devoted to his family, and a loyal friend to his associates and companions.

Memoir of Patrick A. McCarthy (1884–1959)*

By HUGH ROBERTSON, M.D.

VERY few of the many friends of PATRICK A. MCCARTHY suspected that he sprang, not from the verdant od of Eire but from the grim hills of Wales, where he was born in the village of Llantrissant on August 31, 1884. Children of Welsh miners, n the 1880's, had little to look forward to except more coal, and the McCarthys had better things in mind for their active young Patrick, then seven. In 1891 the family migrated to America and settled with friends in Elizabeth, New Jersey.

Life was very simple for Patrick McCarthy; he couldn't buy what he wanted, so he worked or it. This formula began operating with after-school work at the age of twelve and continued until his death sixty three years ater. Each achievement represented the completion of an episode of hard work, and sparked the attack on a new objective. Heavy abor is conducive of sympathy for other strugglers, so during his lifetime Patrick McCarthy helped and encouraged a host of ambitious youngsters. On his way home from St. Patrick's School young McCarthy would pass Froelich's *Deutsche Apotheke* (still operating in Elizabeth, New Jersey). Here was his first contact with Medicine, first as an errand boy, then as an assistant who soon earned a certificate as a Qualified Assistant in Pharmacy.

From the drug store to medical school was not much of a jump; in 1904 Patrick A. McCarthy was listed as a first-year student at the College of Physicians and Surgeons in Baltimore (now the University of Maryland). But two years later the fame of William W. Keen proved more of a temptation than McCarthy and his class-mate Jack Laughery could resist, so 1906 found the two enrolled at Jefferson Medical College, where they graduated in 1908.

In 1907, the year before McCarthy graduated, Dr. Keen retired as Gross Professor of Surgery at Jefferson, and a new star was born—*John Chalmers Da Costa.* After graduating from Jefferson in 1908 McCarthy interned at Jefferson Hospital, but aside from a year spent in a residency at the Lying-in Hospital in New York, all the rest of his lifetime was spent in or near Jefferson and his idol, "Jack" Da Costa. He was Chief Resident at the old Philadelphia Municipal Hospital in 1912, but soon joined the staff of St. Mary's Hospital, where he rose from Clinical Assistant to Chief-of-Staff during his long and active life. For a while he was a Chief of Surgery at Philadelphia General Hospital but his real loves were St. Mary's, (where he did amazingly complex vascular and neuro surgery), and Jefferson (where he worked and taught on the staff of John Chalmers Da Costa).

On January 10, 1911 he married Elizabeth Anderson, a delightful Scottish girl who bore him two daughters, Ruth, now married to Dr. John F. Gordon, (a Philadelphia surgeon), and Elizabeth, (now married to Mr. Ed Maguire of Baltimore). Mrs. McCarthy died several years before her husband was struck down by a cerebral accident in 1958. Friends and associates rallied with inspiring devotion to do what they could for a proud and confident man, now helpless and entirely dependent; he survived for twenty dreary months and died on October 3, 1959, aged seventy-five years.

Patrick McCarthy was a quiet man. The most striking fact about him was his humility. He cared not the slightest for fame or rank. He did really remarkable surgery, much of it in advance of his times, but seldom reported his work or wrote papers. He was present at nearly every important meeting and convention, keenly observant but inconspicuous and silent. His unbounded hidden charity was known only by its recipients.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of Charles Leonard Brown (1899–1959)*

By THOMAS M. DURANT, M.D.

DR. CHARLES L. BROWN, distinguished internist, educator and medical administrator, died at the Jersey City Medical Center on December 4, 1959. His untimely death at the age of 60 is a great loss to the cause of medical education and to the countless persons who knew him personally as a warm and devoted friend. He had suffered from his final illness for nearly two years, yet characteristically he ignored it and continued active in his service to humanity until the very end.

Dr. Brown was born in Metropolis, Illinois, April 27, 1899 and received his medical degree from the University of Oklahoma in 1921. He began his career as medical educator in 1923 when he became Instructor in Pathology at Harvard, followed by a teaching fellowship in the same university from 1925 to 1927, and service as Instructor in Medicine the following year. During this period he was closely associated with the late great internist, Dr. Henry A. Christian, as office assistant. Dr. Christian's high opinion of him is evidenced by the dedication of his editions of the Osler text of Medicine to him along with two other assistants who also had attained eminence. A pupil of Sir William Osler, Dr. Christian spoke of Dr. Brown as "a next in descent in this medical heritage". While at Harvard, Dr. Brown published with Dr. Samuel A. Levine an outstanding monograph on the subject of coronary thrombosis.

In 1928 Dr. Brown was appointed Assistant Professor of Medicine at the University of Michigan where his ability as a teacher and his qualities as a physician became immediately apparent to the faculty and to the students. From 1929 to 1935 he was Associate Professor at that institution.

Philadelphia first came to know Dr. Brown's unusual qualities when he became Professor and Chairman of the Temple University Department of Medicine in 1935 and, under his inspiring leadership, this department achieved a prominent position among the outstanding departments of the country. He remained at Temple until 1946 when he became Dean and Chairman of the Department of Medicine at Hahnemann. Those who worked with him at Temple have much for which to thank him because of the inspiration and leadership he provided and because of the high ideals he set for himself and his associates.

Following a nine-year period at Hahnemann, Dr. Brown in 1955 accepted the responsibility for organizing, as Dean, a new medical school at Seton Hall, Jersey City, New Jersey. He took this position as a challenge and as an opportunity to make another outstanding contribution to medical education. The effort required for the accomplishment of this purpose was tremendous, but, in characteristic fashion, he worked night and day in wholehearted devotion to the task. He was largely responsible for the initial admission policy and procedures, the curriculum and the selection of an excellent faculty. The students came to know him not only as Dean but as a friend and as one always available for discussion of their problems. Though he no doubt knew that his days were numbered he did not spare himself in his drive toward accomplishment of his high objective. It is most unfortunate that he could not have been spared to witness the graduation this year of the first class admitted by him to the school. As a tribute to Dr. Brown, no successor will be appointed until after the June graduation ceremony so that he may still be listed as Dean of that class.

* Read before the College of Physicians of Philadelphia, 2 March 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

During the many years when Dr. Brown was active in the practice of Medicine he was well known for his devotion to his patients. His service to them combined in a remarkable fashion the benefits of modern scientific discovery with the human interest of the old-time family practitioner. His patients were far more than a collection of complicated enzyme systems; they were human beings needing solace and comfort from one in whom they could put their trust. There has been, in all probability, no physician more beloved than was this one.

Dr. Brown was elected a Fellow of the American College of Physicians in 1929, and of the College of Physicians of Philadelphia on May 11, 1936. He was the eighty-fourth President of the Philadelphia County Medical Society, during the 1944–1945 term, and received the Strittmatter Award of that organization in 1950.

He was also a member of the American Society for Clinical Investigation, the American Gastro-Enterological Association, the Sydenham Medical Coterie of Philadelphia, Alpha Omega Alpha and many other organizations. He served very ably on the Eleventh, Twelfth and Thirteenth Revision Committees of the United States Pharmacopeia, an illustration of the interest he always displayed in therapeutics, and for which he was widely known and hailed as a consultant.

Dr. Brown is survived by his widow, the former Ruth McAllister Jamison, and two daughters, Mrs. Janet Emory of Whippany, New Jersey, and Mrs. Martha W. Yancovich, now residing in Germany, and three grandchildren. Mrs. Brown was a devoted wife and a true helpmeet to her husband throughout his arduous and eminent career.

Medicine has lost an outstanding man in the passing of Dr. Charles L. Brown. His influence will be sorely missed, but the good that he has done will live after him in the lives of his students and associates who are better physicians because of their contact with him.

Memoir of Edward Weiss (1895–1960)*

By O. SPURGEON ENGLISH, M.D.

I ASK you to join me in paying tribute to Dr. Edward Weiss, honored colleague and devoted friend, in the Hall of the College of Physicians this evening. All of us here knew his attributes well—we knew him as an alive, vibrant personality. It is with sorrow, then, that I ask you to consider with me the great and wonderful qualities that made him the man he was.

Edward Weiss was a quiet, dignified, unassuming but dedicated man—dedicated to the idea of man's worth and his right to his own personal concept of living. He early saw the interaction of man's personality in health and disease. It interested him intensely. He changed the direction of his career considerably for this idea. Its pursuit in psychosomatic medicine was his vocation, his inspiration, and often the source of his pleasure and satisfaction in living.

Although he was a man of quietness, his ability to fire the imagination inspired many a young man to broaden his horizons. His warmth was felt by everyone. There was never a time when he was too busy to listen with a ready ear and a constructive thought. His urgency was to understand and no one was too unimportant for him to listen to. How many times we would see him in hospital halls, his head half turned, listening with bemused patience to a story he surely had heard a hundred times before from a hundred different patients.

He believed in the patient as a combination of body and mind working together, and was one of the first to teach that understanding illness and sick people consisted of something more than a knowledge of organic disease processes but included a knowledge of emotional processes within that body as well.

Edward Weiss was a pioneer. He had creativity and the discipline to channel his ideas. From his fertile mind developed many of the first clinical evidences that emotional factors do complicate and add to the burden of physical disease. He could discuss, arrange, and teach these pieces of evidence in an interesting and convincing manner.

Edward Weiss was a man of highest integrity and honor. He studied at Jefferson Medical College, graduating there in 1917. After many years of service at Jefferson he was appointed to Temple University School of Medicine as Clinical Professor of Medicine in 1932. In 1933 he began working on novel clinical problems at the medical school. He held what was called a medical-psychological conference which was a teaching exercise for senior medical students. It consisted of the presentation of patients from the medical wards who were studied psychologically as well as medically. From this idea and the case material presented, the book "Psychosomatic Medicine" emerged. It has been translated into many languages and has been used as a text book and reference book for many years and through many editions.

Edward Weiss served as one of the founders and as one of the first presidents of the American Psychosomatic Society. He was a member of the Family Service of Philadelphia and a Lecturer at Bryn Mawr College. He was a Fellow of the American College of Physicians the College of Physicians of Philadelphia (elected 1923), and a member of the American Society for Research in Psychosomatic Medicine. He acted as Chairman of the latter's Research Coordinating Committee for many years. His most recent work was a popular book called, "Don't Worry About Your Heart", published in February, 1959 by Random House. Other publications included numerous medical papers and articles on the

* Read before the College of Physicians of Philadelphia, 6 April 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

heart, personality and psychosomatic manifestations, and books such as, "Emotional Factors in Cardiovascular Disease", published in 1951, "Cardiovascular-Renal Disease" in 1940, "Practical Talks on Kidney Disease", in 1937, and "Diagnosis of Congenital Cardiac Disease" (with Dr. Maude Abbott), in 1928.

Edward Weiss lived a full life in his sixty-four years. We mourn his passing with a deep sense of loss. May this brief memoir serve as an inspiration to all of us here in the College of Physicians of Philadelphia. We shall long cherish his memory. We hope that this expression of our respect and admiration will convey to his beloved wife and children the high repute with which he was held, and will in some measure alleviate their sorrow which is also felt by every member here tonight.

TRANSACTIONS & STUDIES
of the
College of Physicians of Philadelphia

Volume 28
(Fourth Series)

Number 3
(January 1961)

Observations and Reflections on the Lymphatic System[1]

By H. S. MAYERSON, PH.D.[2]

IT IS a privilege for me to be here this evening to present the 80th Mary Scott Newbold lecture. I understand that this lectureship is the only one of your eight current lectureships that does not bear the name of a physician, or was not founded by one. I should like to pay my tribute to Mr. Clement B. Newbold for his vision and his appreciation of the importance of cross-fertilization of ideas in stimulating scientific and medical progress. I am grateful to him and to you for providing this occasion for meeting of old friends, for good fellowship and, perhaps more important, for my telling you something of the work which our group has been doing for a number of years. This is always a pleasant task.

Our work has been concerned with the interchange of substances between plasma and lymph. Currently, we are particularly interested in specific functions and characteristics of the lymphatic system as they are manifest under a variety of physiologic and non-physiologic situations.

Before I go into the details of our work, however, it would seem appropriate to consider the general functions of the lymphatic system. The clinician is prone to regard the lymphatic system, lymphatics, lymph nodes and lymphocytes as a mechanism defending the organism against infection. This is a mechanism of unquestionable importance. He is less likely to regard it from a physiologic point of view, as a vital system concerned with the maintenance of homeostasis. I should like to remind you that the blood capillaries are a closed system of vessels; the blood only comes in actual contact with the cells of the tissue in the liver and perhaps in the spleen. The cells everywhere else are bathed by tissue or interstitial fluid which acts as an intermediary, supplying nutritive materials and receiving the products of metabolic activity. Phylogenetically, the need for the lymphatic system arose as soon as a closed cardiovascular system developed. In the mammal, the necessity of providing a high pressure system to insure an adequate supply of oxygen to the tissues created a situation favoring the transudation of fluid from the capillaries. The role of this mechanism was minimized by the increase in plasma proteins which exerted an oncotic pressure, but there still remained the problem of clearing the tissue spaces of substances

[1] Mary Scott Newbold Lecture LXXX, 5 October 1960.

[2] Professor and Chairman, Department of Physiology, School of Medicine, Tulane University, New Orleans 18, Louisiana.

which had leaked out or which were not absorbed by the blood.

Knowledge of the lymphatic system goes back to the seventeenth century. Aselli in 1622 demonstrated "lacteals" in the mesentery of a dog and at a later date had the opportunity of observing these channels in a criminal who had been executed following a large meal. Rudbeck and Bartholin separately described lymph vessels at about the middle of the seventeenth century and are usually considered to be the co-discoverers of the lymphatic system. Much has been done since 1650 and considerable information has been accumulated concerning the embryology and distribution of the lymphatics, as well as their function. There is still, as we shall see, much to be learned and many questions to be answered.

At the latter part of the last century and at the beginning of the present one, Professor E. H. Starling, working in London, published his extensive experiments on lymph and exchange of fluid and substances between plasma and lymph (1). Fundamental to his concepts was the assumption that large protein molecules do not readily pass through the capillary membrane. What was lost sight of until the last decade was that although protein does not pass out *readily*, it does pass out and that in the course of a day some 50 p.c. or more of the total circulating protein escapes from the blood vessels (I shall have more to say about this later). This extravascular protein cannot be directly reabsorbed into the blood capillaries and hence must return by way of the lymphatics. The mechanisms involved are of fundamental importance and are an expression of the general function of the lymphatic system: the maintenance of a proper tissue environment. Not only do the lymphatics return protein, but they serve as the mechanism for clearing the tissue spaces of fluid, thus preventing undue increases in the tissue fluid pressure. At the same time, the lymphatic return of protein and fluid is an important factor in plasma volume maintenance. Lymph transports vitamin K from the intestines to the blood stream (2) and is the major if not the exclusive agent for the transport of absorbed long-chain fatty acids (3). There is also the suggestion that some enzymes may be transported to the blood stream via the lymphatics (4).

I should also like to remind you that lymph vessels are derived from veins. To quote Florence Sabin (5), who did so much in this field, "Lymphatics are modified veins. They are vessels lined by an endothelium which is derived from the veins. They invade the body as do blood vessels and grow into certain areas; their invasion of the body is, however, not complete, for certain structures never receive them. The lymphatic capillaries have the same relation to tissue spaces as have blood capillaries. None of the cavities in the mesoderm, such as the peritoneal cavity, the various bursae and serous cavities form any part of the lymphatic system. The lymphatic endothelium once formed is specific. Like blood vessels, the lymphatics are for the most part closed vessels." It may also be well, at this point, to point out that the lymph nodes are not fundamentally an integral part of the system of lymph vessels, since lymph nodes are not found in fishes, amphibians and reptiles, and only to a limited extent in birds. It is therefore probably incorrect to consider the lymphatics proximal to the nodes as ducts of these glands, but rather to view the nodes as forming interruptions of the vessels, a situation brought about by special conditions in mammals, the reasons for which are not clearly apparent at this time.

The time at our disposal will not permit any detailed discussion of the anatomy and distribution of lymphatics or of the composition or characteristics of lymph. These are adequately presented in the excellent publications of Drinker and his colleagues (6) and particularly in a recent monograph by Yoffey and Courtice (7).

I would, therefore, like to go on to tell you of the results of some of our explorations and share with you the concepts and ideas they have produced. This has been a group operation in which my colleagues, Dr. Karlman

Wasserman and Stephen J. LeBrie have been vitally concerned, aided and abetted by a number of eager medical students whose industry, zeal and competence have been (and continue to be) important factors in opening new pathways and sustaining our enthusiasm in the work.

I suppose that every investigator, at some time, has asked himself "How did I ever get into this mess?" Let me tell you how I did. One afternoon some 15 years ago, I was having coffee with Dr. Champ Lyons, who was then at Tulane in the Department of Surgery. We got around to some of his war experiences in the Mediterranean theater where he had given large transfusions to wounded men and followed plasma volumes with the blue dye, T1824. His data indicated that much of the transfused volume was not being retained. He wanted me, as a physiologist, to tell him what was happening. I knew that the problem of "lost plasma" was not a new one but I had no satisfactory answers. So we decided to try to get some answers and in no time at all, as you can guess, a project was born. We applied for funds from the Research and Development Division (now Command) of the Surgeon General's Office, received them, and, I should add, are still being generously and sympathetically aided with funds, for which we are sincerely grateful.

I shall pass over rapidly the first phases of the project. Fortunately for us, isotopes were just becoming available and our first job was to develop methods of accurately measuring blood volumes, using human serum albumin iodinated with radioactive iodine (I^{131}) for plasma volume and red cells labelled with radioactive phosphorus (P32) for measurement of red cell volumes. Armed with these reasonably quantitative methods and with the assistance of two fellows, John H. Clark and Woodrow Nelson, who came back from the war for training in surgery, we invaded the clinics. Few patients were sacred. We became particularly interested in the data from chronically debilitated patients, who usually showed low blood volumes and we suggested that these individuals were suffering from "chronic shock"(8). In doing so, we brought down the wrath of colleagues, as some of you recall, who complained that modifying an indefinable term like shock was "confusion worse confounded." However, I do think it emphasized the importance of actually measuring blood volumes in these and other patients rather than relying solely on the usual concentration measurements. We made many other interesting observations, but most important, we confirmed the previous empiric observations that when large quantities of blood were given, the plasma appeared to leave the blood stream and only the red cell portion remained. This implied that the plasma proteins were leaking out of capillaries. But capillaries, as I indicated previously, were supposed to be relatively impermeable to molecules as large as protein. It is true that Drinker (6) had been insistent that so called "normal" healthy capillaries leaked protein. Curiously enough, it was a hard idea to sell and most textbooks of physiology continued to hedge the issue by saying that significant protein leakage could occur, but only when capillary permeability had increased over "normal" for one or another reason.

Drinker mustered considerable evidence to support his argument but much of it was necessarily indirect, for he had no satisfactory way of labelling plasma proteins and following their leakage from capillaries. Time had given us an advantage. With the availability of isotopes, it was apparent that we could label proteins and not only quantitatively follow their disappearance from the blood stream but could also trace them to lymph. This then became the next phase of the problem—to learn what we could about the permeability of blood capillaries. In doing so, we have accumulated considerable information and interest in the lymphatic system and are continuing to explore this system in a variety of experimental approaches.

Our early work, as I have implied, was concerned with the permeability of capillaries to albumin and globulin. We injected radio-

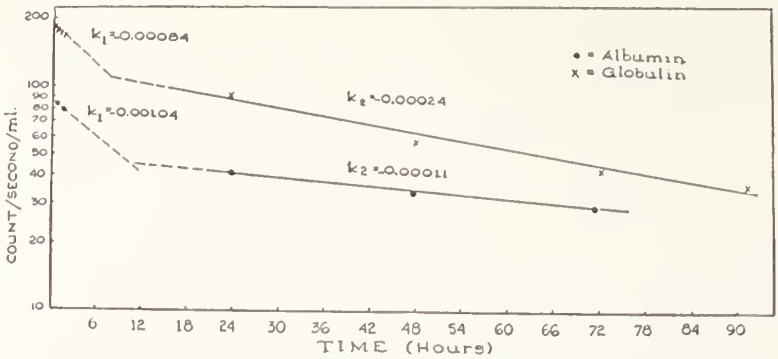


FIG. 1. Semi-log plot of concentrations of radioactive iodinated human serum albumin (lower curve) and radioactive iodinated bovine gamma-globulin (upper curve) in the plasma of dogs. The homologous proteins show quantitatively the same disappearance. The K_1 is the value of the first slope and the K_2 is the value of the second slope of the log plot. The intercept of the extrapolated slopes indicates the approximate equilibrium times.

active iodinated serum albumin and globulin intravenously into dogs, measured their disappearance from the blood stream and their appearance in thoracic duct lymph (9) (Figure 1). (I should like, at this point, to express my gratitude to the American Red Cross for its continued generosity in making albumin available to us over these many years.)

Iodinated albumin and globulin, as given intravenously in our experiments, distribute themselves rapidly throughout the vascular system. They begin to leave the plasma immediately after injection and the disappearance proceeds in a uniform exponential manner for at least 6 to 8 hours. Thereafter there is a definite change in rate at which the labelled proteins leave the plasma. The proteins now leave at a much slower rate but the disappearance is still exponential and continues in this manner for at least 5 days, the longest period studied in any of our experiments. Calculation of the exponential constants (k values) for the rate of disappearance of the radioactive iodinated proteins yields average values of $-.00092$ and $-.00077$ for the first slopes (k_1) of the disappearance curves of albumin and globulin respectively. The second slopes (k_2) have average values of $-.00010$ for albumin and $-.00025$ for globulin.

We believe the first slope of the plasma disappearance curve (k_1) to be primarily an expression of the movement of the radioactive protein into the interstitial fluid spaces and the second slope (k_2) to represent the rate of metabolism of the protein. Our results thus show that although globulin leaves the circulation much more slowly than does albumin, it is metabolized 2.5 times faster than albumin. The latter observation has also been made by other investigators using different approaches (10). The time for complete metabolic turnover for plasma globulin is 66 ⅔ hours and for plasma albumin is 166 ⅔ hours. The time for complete turnover due to leakage from capillaries is 33⅓ hours for globulin and 21 hours for albumin.

It is difficult to state the earliest time of appearance of labelled protein in the lymph (Figure 2). This is primarily due to the difficulty of obtaining a sufficient amount of lymph for analysis within the first 3 or 4 minutes after injection. There is no question but that it is present in thoracic duct lymph in small amounts in from 5 to 8 minutes after its intravenous injection. The accrual is rapid at first, but the rate of accrual decreases as the concentration increases until about 7 to 13 hours after the injection.

Calculation of specific activity (radioactive protein in counts per 100 ml. divided by concentration of native protein in grams per 100 ml.) shows that an equilibrium of specific activities between plasma and lymph occurs sometime between 7 to 13 hours for either

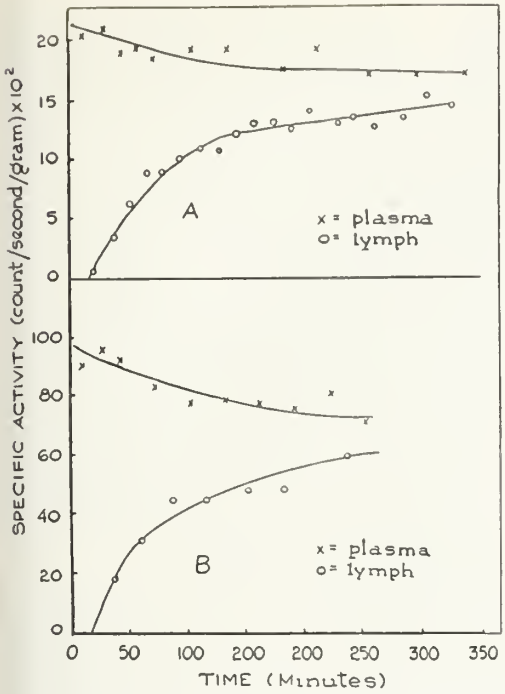


FIG. 2. Disappearance of radioactive protein from the plasma and its appearance in the thoracic lymph of dogs. A = albumin. B = globulin.

protein. Samples of lymph and plasma analyzed after this time show that specific activities in the two compartments remain equal and decline at the same slow rate. This equilibrium between specific activities of the protein systems denotes that the labelled albumin and globulin has now become evenly distributed between plasma and lymph protein. Once this equilibrium is established, it is maintained. Our longest experiments lasted for 5 days but it may be presumed that the equilibrium would persist for as long as there was radioactive protein present.

Drinker (6) felt that the fluid in a lymphatic trunk is essentially interstitial fluid since no anatomic structure which might act as a semipermeable membrane has been demonstrated at the entrance to the lymphatic vessels. If lymph is considered to be a direct product of plasma, our data for the appearance of the iodinated albumin in lymph should yield the familiar "decay" type of curve. The curve we obtained, as shown in the previous figure, is, however, not a "decay" type of curve but a "growth" type of curve. This "growth" type of curve, as we have shown in detail in one of our publications (11), is the type of curve which we would expect to find if protein filtered from the capillaries and mixed with another protein pool before being taken up in the lymph ducts. We visualize this pool as the protein in the pericapillary interstitial space before absorption by the lymphatics.

In the early experiments, we sought to increase the flow of lymph by priming the animals with saline infusions. We soon realized that this was distorting our data and decided to study the effects of infusing saline in varying amounts on the leakage of proteins from the capillaries (12). If we infused moderate amounts of saline equivalent to from ½ to ⅔ the plasma volume, there was no consistent or significant change in albumin disappearance from the blood stream or its appearance in lymph. On the other hand, when the infusion volumes were made larger, there was a definite increase in the rate at which albumin was leaking from the blood stream. The leakage rate was now 3 to 4 times the control rate. After an infusion of a liter of saline, the total plasma albumin filtered through the capillaries in 6 hours as compared to 20 or 21 hours when no infusion was given. The large saline infusions, however, resulted in increased lymph flow (Figure 3A) as well as an increase in albumin flow. (Figure 3B). It became obvious that the eventual level of total circulating plasma protein was determined by a number of factors. Infusion results in the filtration of a more dilute protein solution than that filtered before the infusion, but which has a greater albumin content as well as a larger volume. This then mixes with the relatively more concentrated pre-infusion interstitial fluid, so that the concentration of albumin in lymph after the infusion is intermediate between that of the interstitial fluid formed before the infusion and the newly formed interstitial fluid. The eventual effect of an infusion

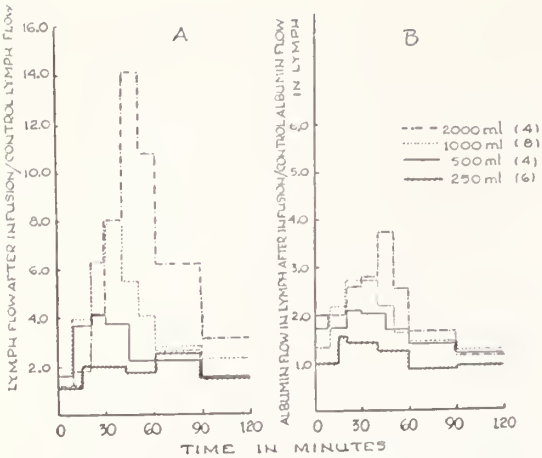


FIG. 3A. Ratio of lymph volume flow (milliliters per minute) after the start of the infusion to the preinfusion (control) lymph volume flow plotted against the time after the beginning of the infusion. The 250-ml. infusions lasted approximately 8 minutes, the 500-ml. infusions lasted 15 minutes, the 1000-ml. infusions lasted 30 minutes and the 2000-ml. infusions lasted approximately 1 hour. Average control lymph flow for these experiments is 0.5 ml/minute.

FIG. 3B. Ratio of lymph albumin flow (milligrams per minute) after the start of the infusion to the preinfusion (control) lymph albumin flow plotted against time after the beginning of the infusion for the same experiments as in figure 3A. Numerals in parentheses to the right of the infusion volumes are the numbers of experiments which were averaged in each group. Average control albumin flow for these experiments is 8.5 mg/minute.

on the total plasma level will thus depend on 1) the degree of distention of the interstitial space as a result of the infusion since a greatly distended interstitial space may hold much of the protein which ordinarily might have gone back to the circulation via the lymphatics; 2) the rate (and amount) of albumin leaving the capillaries; 3) the amount of albumin present in interstitial fluid available for mixing with the plasma filtrate; and 4) the rate of lymph flow. If the lymph does not return to the venous system or if the amount disappearing from the plasma is greater than the amount returned via lymph, the plasma albumin will be decreased and remain low until the usual conditions of flow are reestablished. Our results emphasize that this is not a mobilization of cell protein, as has been suggested in the literature (13, 14) but involves primarily the movement of interstitial fluid protein. With our technique, addition of new protein from any source drained by lymph coming to the thoracic duct would be apparent as a lowering of specific activity of thoracic duct lymph protein. We have never observed such a decrease.

We obtained very much the same results with other infusion solutions such as dextran, blood and plasma. The important factor seemed to be the volume of the infusion or, more precisely, the relationship of the infusion volume to the capacity of the circulatory system. We have obtained data from many types of experiments supporting this concept but a full discussion of this intriguing relationship would lead us too far afield. One set of observations is, however, pertinent.

In connection with some of our work concerned with the effectiveness of dextran as a plasma extender, we were fortunate in having made available to us by the National Research Council, eight dextran fractions of average molecular weights between 10,600 and 412,000. When we gave small infusions of these solutions (5 to 10 ml. per kilo of body weight) and determined the ratios of dextran concentration between thoracic duct lymph and plasma we obtained data which indicated a definite relationship between the size of the molecule and its leakage from the capillaries (15). The lowest molecular weight fraction (average 10,600) showed a concentration ratio of approximately unity and the highest molecular weight fraction (average 412,000) showed a ratio of approximately 0.26. These results were in accord with those postulated by well-known molecular sieving concept elaborated by Pappenheimer (16) who suggested that, during ultrafiltration through isoporous membranes, the filtrate/filtrand ratio is not necessarily unity or zero but may be some intermediate value which depends on the size of the molecule relative to the size of the membrane pore and the filtration rate. Molecular sieving is thus conceived as due to steric hindrance and viscous drag of the large molecules during ultrafiltration. Pappenheimer showed

that the filtrate/filtrand ratios decrease (greater decrease of molecular sieving) as the filtration rates increase due to the increased role of viscous drag during high rates of filtration.

In our experiments, as I indicated above, infusion of small volumes gave results which were in accord with Pappenheimer's concept. On the other hand, when we increased ultrafiltration by infusing large volumes of 6 p.c. dextran solutions or 5 p.c. serum albumin, 40 mg. per kilo of body weight, which in the average size dog is roughly equivalent to his plasma volume, lymph/plasma concentrations for albumin and all molecular weight fractions of dextran increased and tended to approach unity. The changes in lymph/plasma concentration ratios were greatest for the high molecular weight fractions and occurred in spite of increased lymph flows. On the assumption that lymph is a filtrate of plasma, these findings of an increased ratio of concentration in filtrate and filtrand with increasing filtration rate were contrary to the concept of molecular sieving. We interpreted the results of large infusions as due to stretching of the pores so that large molecules now encountered less resistance and passed through capillary membranes in higher concentration even though the filtration rate was increased.

Grotte (17), working in Upsala, Sweden, on more or less the same problem, objected to our conclusions (correctly, I believe) because they were based on data derived from thoracic duct lymph. He pointed out that thoracic duct lymph in the anesthetized dog is derived mainly from the intestines and liver and that the great permeability of the liver may constitute a special outlet mechanism, i.e. after large infusions of colloidal solutions, the increase in macromolecular concentration measured in thoracic duct lymph may be due to a relatively greater increase of lymph flow from the liver than from the other souces of thoracic duct lymph having a lower permeability to macromolecules. To answer this objection, we undertook to repeat the experiments but collected lymph from the right duct (18). In the quiescent, anesthetized dog the amount of lymph collected from the right duct expresses the lymph delivery from the contracting heart and the moving lungs (19). Right duct lymph resembles cervical and leg lymph in that it has a low protein concentration (0.5–3.5 gm. p.c.).

Although Drinker described a procedure for isolating and cannulating the right lymph duct which seemed simple enough, in my hands, this was no easy task. I had reached the point where I could find the right duct reasonably well at the beginning of a summer session when we usually get an influx of bright young medical students who want to spend the summer learning to do research. One of these, Hoke Shirley, allowed that he would like to work in the laboratory but only if we could challenge him with a really difficult problem. He had a buddy, Gordon Wolfram, who, he said, was equally good. I sold them the right duct problem then and there. When they were ready to do their first experiment, I carefully absented myself from the laboratory and came back later in the day prepared to console them and hold their hands. But you may have guessed what happened. They not only did a most successful experiment that day but did six successive successful experiments before they missed.

The results which they obtained are shown in next several figures (figures 4 and 5) and illustrate a typical experiment. Two milliliters per Kg. of body weight of 12 per cent dextran of average molecular weight of 255,000 (NRC fraction 7) were injected simultaneously with 1 ml. radioactive iodinated albumin. Figure 4 illustrates the disappearance of injected radioactive iodinated albumin from the plasma and its appearance in thoracic and right duct lymphs. Initially, lymph contains a small amount of unlabeled albumin but, with time, labeled albumin leaking from the capillaries appears in the lymph and a "steady state" is reached in which the lymph/plasma ratio remains essentially constant. The concentration of radioactive iodinated albumin in right duct lymph is considerably less than in thoracic

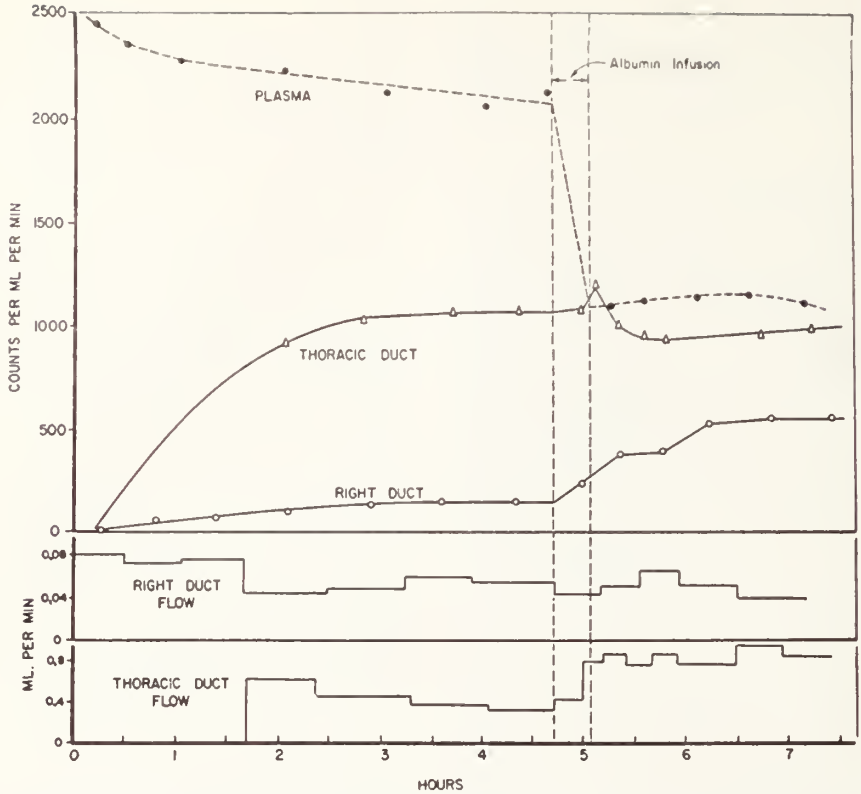


FIG. 4. Concentrations of radioactive iodinated albumin in plasma, thoracic and right duct lymphs and lymph flows before and after infusion of 40 ml./Kg. of a 5 per cent albumin solution. Two ml./Kg. of 12 per cent dextran (average M.W. = 255,000) and 1 ml. radioactive iodinated albumin injected at zero time.

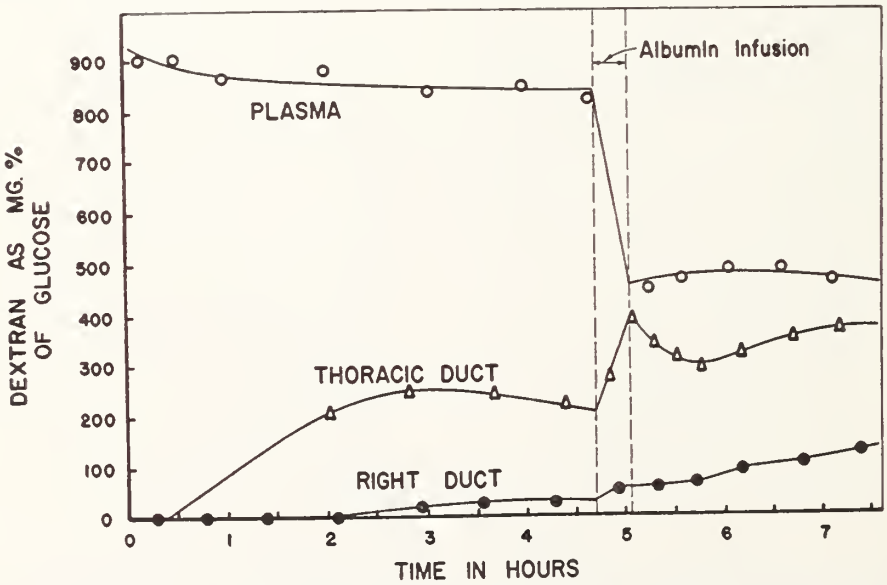


FIG. 5. Concentrations of large molecular weight dextran (average M. W. = 255,000) in plasma, thoracic and right duct lymphs before and after infusion of 40 ml./Kg. of a 5 per cent albumin solution. Same experiment as shown in Figure 4.

duct lymph. In the experiment shown in Figure 4, the lymph/plasma albumin ratio for right duct lymph was 0.077 whereas for thoracic duct lymph it was 0.508. These data suggest that capillaries of the lung and heart are much less permeable to albumin than are capillaries of liver and intestine.

Four hours and forty minutes after the original injection and after a "steady state" had been reached in thoracic and right duct lymphs, a 5 per cent serum albumin solution was infused (40 ml. Kg.). There was an immediate sharp drop in plasma radioactive iodinated albumin concentration, a slight decrease in thoracic duct lymph concentration and a marked rise in right duct lymph concentration. Significantly, the increased concentration in the latter occurred with minimal (or, in other experiments, with an increase) in right duct lymph flow. The right duct lymph/plasma concentration ratio rose from 0.077 to 0.515. In the thoracic duct, lymph flow was approximately double the pre-infusion level while the lymph plasma concentration ratio increased from 0.508 to 0.905. Thus, for both right and left duct lymphs, the lymph/plasma concentration ratios increased significantly after the infusion. This can occur only if capillary porosity has increased, for if capillary porosity remained constant, lymph/plasma concentration ratios should decrease, since (a) the plasma concentration is reduced to approximately one-half of its original level and (b) molecular sieving would be enhanced due to the higher filtration rate.

The pattern of change for the high molecular weight dextran (figure 5) is similar to that of radioactive iodinated albumin except that the changes are of greater magnitude. Control lymph/plasma dextran ratios were lower than for albumin, 0.031 and 0.266 for right and thoracic duct lymph, respectively, a reflection of the larger molecular size of the dextran as compared to albumin. Following infusion, plasma dextran concentration dropped from a pre-infusion level of 820 mg. per cent to 450 mg. per cent and remained at approximately this level for the rest of the experiment. Thoracic duct lymph showed a marked increase in dextran concentration, rising from 220 mg. per cent before the infusion to 280 mg. per cent at the end of the experiment. The lymph/plasma ratio increased from 0.266 to 0.770. Particularly significant was the increase in dextran of right duct lymph, which was approximately 20 mg. per cent before the infusion and rose to 120 mg. per cent at the end of the experiment, approximately two and one-half hours after the infusion. The curve of concentration was still rising at this time. The dextran lymph/plasma concentration ratio for right duct lymph rose from 0.031 to 0.288.

All of the data from the right duct experiments parallel those previously obtained from the thoracic duct and the changes are opposite to those predicted by the molecular sieving phenomenon. With the exception of the experiment shown in figures 4 and 5, the large 40 ml. per kilogram body weight infusions were always followed by significantly increased lymph flows from the thoracic and right ducts which persisted during the post-infusion period when plasma volumes were falling. The increased concentrations of albumin and dextran in lymph following the large infusions thus cannot be explained as the result of movement of water into the blood stream leaving the macromolecules more concentrated in the lymph.

These results, we believe, answered Grotte's criticisms, since the abdominal viscera were not implicated. They emphasized the correctness of our previously formulated concept that infusions producing plasma volume expansion cause capillary "pores" to enlarge or stretch with a resultant increased leakage of large molecules. This was a possible explanation for the "lost plasma" phenomenon and the answer to the question which stimulated the beginning of the work some ten years previously. Large infusions not only engorge the capillaries and raise filtration pressure but the pores stretch and permit increased leakage of macromolecules.

But while we were answering some questions we were raising many more. It has long been known that the protein concentration of lymph from different areas varied; thoracic duct

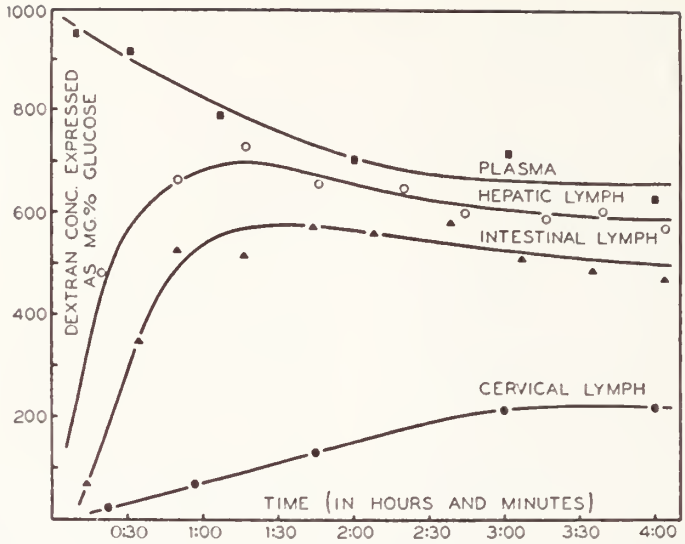


FIG. 6. Typical experiment showing disappearance of dextran (N.R.C. fraction #2, average M.W. = 35,000) from plasma and its appearance in lymph of various areas.

lymph having a concentration approximately ⅔ that of plasma, whereas, as previously noted, right duct lymph contained only about ½ to ⅓ or less protein. Furthermore, in our work with dextran fractions, as I stated above, we found that plasma to lymph concentration gradients for varying molecular weight dextrans and protein showed a direct relationship between gradient and molecular weight. All sizes of dextran fractions including that with an average molecular weight of 412,000, the largest molecules studied, penetrated capillaries and were present in thoracic duct lymph. We postulated at that time that all capillary beds which permit leakage of dextran with molecular weight of 51,000 also permit leakage of dextran with molecular weight of 412,000 and that all major capillary beds through which macromolecules leak have the same pore size distribution although they may differ with regard to total pore population. On the other hand, when we calculated volumes of distribution of these fractions, we found higher volumes of distribution for the smaller molecular weight fractions (average M.W. = 10,600 and 35,000). This left open the question as to whether the same capillary beds leak dextran of molecular weight of less than 51,000 and no dextran of higher molecular weight.

By this time our two students, Shirley and Wolfram, had become quite adept at getting into lymphatics, so they went on with us to do a somewhat heroic type of experiment, simultaneous collection of lymph from the thoracic, hepatic, intestinal and cervical ducts. In a few instances, they added right duct lymph collection just to prove they still could do it. (20)

We infused, simultaneously, 2 ml. per kilogram of body weight of a 12 p.c. solution of the dextrans of each different molecular weight and a milliliter of radioactive iodinated serum albumin and took samples of lymph and plasma at appropriate intervals and calculated lymph/plasma concentration ratios.

A typical experiment is illustrated in figures 6 and 7. After intravenous injection of albumin and dextran, measurable amounts begin to appear in the lymph within 15 minutes. As the molecules leak out of the capillaries into the peri-capillary space, plasma concentrations fall and lymph concentrations rise. As more and more of the original "non-tagged" lymph (containing no test molecules) is washed out of the lymphatics and replaced by newly

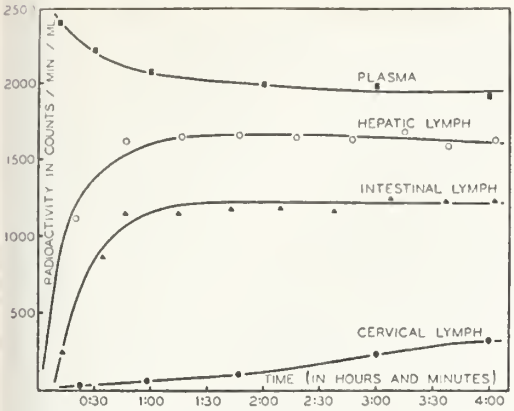


FIG. 7. Same experiment as in figure 6 showing disappearance of radioactive iodinated albumin from plasma and its appearance in lymph of various areas.

formed "tagged" lymph, lymph concentrations further increase and tend to approach plasma levels. When all "non-tagged" lymph is washed out and drained into the great veins, a "steady state" is achieved, and plasma and lymph concentrations decline slowly at a rate dependent on the catabolism of the test molecules. The lymph concentration never reaches that of the plasma except for the smallest dextran fraction of average molecular weight of 10,600.

The lymph concentrations increase at varying rates in different sites, relatively rapidly in thoracic and hepatic lymph and slower in intestinal and cervical lymph. Radioactive iodinated albumin appears in lymph from all the areas studied and the lymph/plasma ratios for albumin for any given capillary bed are quite similar for all animals studied. This is also true of any given fraction of dextran. On the other hand, while all molecular weight dextrans appear in intestinal and liver lymph, only the smaller fractions (average M.W. 10,600 and 35,000) appear in cervical lymph in concentrations greater than $\frac{1}{50}$ of the plasma concentration. At the end of 4 hours, the dextran hepatic lymph/plasma concentration ratios are essentially unity for fractions 1, 2, and 3 and less than 1 for the larger molecular weight fractions. The ratios for intestinal lymph are at approximately unity only for fraction 1 and are smaller for the larger molecular weight fractions.

As indicated above, the time required for lymph concentration to reach steady state values for albumin and dextran varies inversely with the rate of flow. This was also shown by Benson, Lim and Bollman (21) who reported that muscle exchanged albumin slowly between plasma and lymph, intestine about twice as fast and liver nearly six times as fast as muscle. Because of these differences in flow rate, it is not too meaningful to directly compare lymph/plasma concentration ratios from different areas. Differences in filtration factors, reabsorption and hydration also complicate the situation and make direct comparisons of little value. Previous work, as I said before, showed that all lymph albumin is albumin which has leaked through capillaries from plasma and the present experiments showed that albumin was present in lymph from all areas studied. We have, therefore, chosen radioactive iodinated albumin as a common denominator and have related the leakage of dextran to that of albumin in each dog by dividing the lymph/plasma ratio for dextran by the lymph/plasma ratio for albumin and have designated this value as the "Relative Permeability Coefficient" (R.P.C.). Variations in lymph flow, filtration and reabsorption from dog to dog will affect not only the ratio of dextran but also the ratio for albumin. The absolute value of the coefficient will be relatively unchanged.

This approach is supported by the results of our data showing relatively constant values of the R.P.C. for a given area in different dogs. Furthermore, dextran fraction #3, which has an average molecular weight similar to that of albumin, would be expected to yield an R.P.C. value of unity if the concept is valid. We found this to be true in each capillary bed studied.

Calculation of the R.P.C. makes it possible for us to compare permeabilities of a capillary bed from animal to animal, as well as to determine relative pore sizes. The reasoning justifying this statement is detailed elsewhere

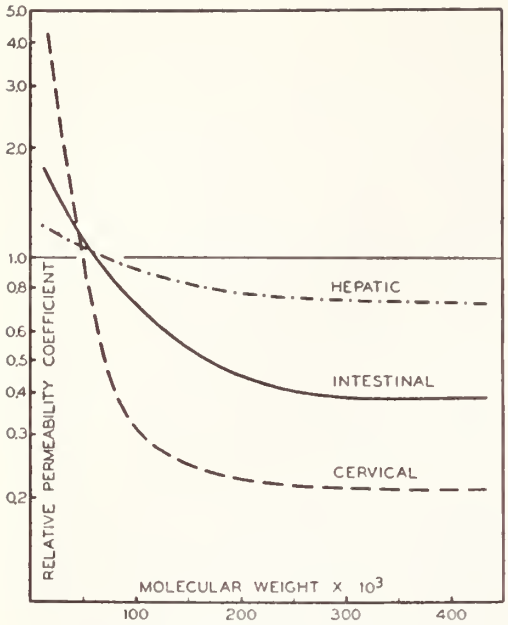


FIG. 8. Curves illustrating relative permeability coefficients for various dextran fractions. Hepatic values obtained from 25 dogs, intestinal values from 26 dogs and cervical values from 24 dogs.

(20). Figure 8 shows relative permeability coefficients for the various dextran fractions. The data for cervical, hepatic and intestinal lymph yield three discreet curves which intersect at a molecular weight of approximately 60,000 and an R.P.C. of 1. The curves possess certain similarities; 1) the R.P.C.'s progressively decrease with increasing molecular weight of dextran; 2) each curve is composed of 2 separate portions. The first portion is curving and falls more rapidly than the second portion (above M.W. 250,000) which is linear and relatively horizontal. The slopes of the first portion of each curve are different in that the cervical curve is steep and falls rapidly, the intestinal curve is less steep and the liver curve has the smallest slope. These curves suggest a bimodal pore population. The first portion of the curves correspond to theoretical curves derived by Renkin (22) from equations based on concepts of viscous drag, molecular sieving and restricted diffusion and suggest that in each of the capillary beds studied there exist a set of pores of uniform size which will allow passage of molecules not greater than about 250,000 M.W. This limit is suggested by the fact that the rapidly falling, non-linear first portions of the curves end at approximately 250,000 M.W. and are continued as the horizontal second portions. The second horizontal portions of the curves represent another set of pores of much larger diameter, so large that they are just as permeable to molecules of average molecular weight of 412,000 as to molecules of 250,000. It is obvious that we have not reached the upper limit of molecular size at which frictional resistance is apparent. The pores are apparently much larger than the largest molecules we used.

The data thus shows that in each area studied the capillary bed is composed of at least 2 sets of pores, one group permitting passage of molecules not greater than 250,000 M.W. (small pores) and a second group (large pores) allowing molecules to pass out of at least 412,000 M.W. The differences in permeability reflected by the 3 R.P.C. curves are due to the fact that in each capillary bed the percentage of total pore area made up of small pores and large pores is variable. For dextran molecules of average molecular weight of 10,600 M.W. the lymph/plasma ratio in every region studied was approximately one. This would signify that this molecular size encounters no frictional resistance as it passes across the capillary walls; in other words minimal, if any sieving is occurring. Stated differently, 100 pc of the pore area in each bed is composed of pores which will allow molecules of 10,600 M.W. to pass through without hindrance. Increased frictional resistance, as the size of the molecule approaches the size of the pore, accounts for the apparent decrease in permeability from 10,600 to 250,000 M.W.

The per cent of total pore area composed of small and large pores may be calculated from the R.P.C. curves. Thus, in the cervical region, the point at which 100 pc of the pore area is permeable to the test molecule of 10,600 M.W., the R.P.C. is 5.0. At a molecular

weight of 250,000 the point at which the area composed of small pores is impermeable to the test molecule, the R.P.C. is only 0.22. At this point, the small pores are passing only molecule-free filtrate, and the large pores are passing fluid containing the test molecule in its actual plasma concentration. The final lymph concentration of the molecule is the result of the mixing of the two filtrates. If this is true, an R.P.C. of 4.4 pc of the original value can only be explained if 95.6 pc of the pore area passes molecule-free filtrate and 4.4 pc of the pore area passes the molecule in its actual plasma concentration. Thus, 95.6 pc of the pore area is composed of small pores (with a diameter allowing passage of molecules not larger than 250,000 M.W.) and 4.4 pc is composed of "large pores", capable of passing larger molecules.

Applying this method of calculation to the other curves, values of small and large pore areas are obtained as follows:

Capillary bed	Small pore area	Large pore area
Cervical	95.6 pc	4.4 pc
Intestinal	78.4 pc	21.6 pc
Hepatic	33.3 pc	66.7 pc

The amount of lymph formed in any given area seems to be directly proportional to the percentage of total pore area made up of large pores. Thus, the hepatic capillaries, much of whose pore area is made up of large pores, are relatively highly permeable and the lymph flow from the liver is several times that from the cervical region where the pore area is composed primarily of small pores.

Less extensive data from similar experiments on right duct lymph shows that the permeability of capillaries of the heart and lung (whose filtrate drains into the right duct) is very low, being slightly less than that of cervical capillaries. The R.P.C. curve has the same general configuration as that of the cervical region but is slightly lower.

Our results and conclusions are similar to those of Grotte (17) but differ in certain details which need not be discussed here. In our discussions and in our thinking, we have followed the classical concept of considering the capillary as a tube penetrated by ultramicroscopic aqueous channels or "pores". Our data, showing that in each capillary bed there exists a "cut-off" point in permeability at about 250,000 M.W. which varies little from bed to bed or from dog to dog, suggests that these channels have functional dimensions and may be considered as "pores" since they behave experimentally as if they are "pores". The similar types of R.P.C. curves obtained from different regions and different dogs also supports the concept. Small molecules (crystalloids) probably cross the capillary membrane by diffusion through these pores. For larger colloid molecules, however, filtration is probably the primary method of transcapillary exchange because of the relatively low diffusion coefficients of these molecules and since net water flow is in the same direction. While water molecules probably exchange very rapidly across membranes by diffusion, net water flow is toward the outside of the capillary as shown by the formation of lymph. Evidence is accumulating which implicates the participation of enzymes and structural alterations as a means of active transport (23). Morphological evidence from electron microscope studies have shown that the structure of capillary walls is complex and variable. Thus, Hall (24) and others (25, 26) have described the existence of pores in glomerular capillaries but their uniform presence in capillaries of other areas is not established. Large pores such as are postulated by our data and that of Grotte should be discernible as definite channels in the electron micrographs but no such processes have been described. Even in the kidney where pores have been described in the endothelial cells there seems to be no evidence for inter-endothelial cement and and so we must abandon the theory proposed by Chambers and Zweifach (27) that the pores of the intercellular cement are the structural basis underlying capillary permeability. Electron microscope studies of endothelial cells have, however, shown the presence of intracellular vesicles of about 650A in diameter

packed tightly in layers facing the pericapillary space as well as the capillary lumen (24, 26). Many of these appear to open at the surface of the cell membrane. It may be that our "large pores" are these vesicles since the horizontal portion of the R.P.C. curves can be conceived as representing a bulk transport system in which there is no restriction to the trans-capillary passage of molecules from 250,000 N.W. to at least 412,000 M.W. The transfer of macromolecules may consist of the material being taken up in a vesicular process and extruded when the process is pinched off. Moore and Ruska (28) have suggested that this process can be better described by the word "cytopemphis" rather than "pinocytosis" in order to convey the idea that substances are being transmitted through the cytoplasm rather than utilized by the cell. The designation of pinocytosis (cell drinking) would be reserved for the situation in which fluid is incorporated by the cell for its own supply.

Having thus accumulated considerable information showing that proteins and other large molecules leak from the blood stream, pass into the lymphatic system and are returned to the venous circulation via the lymph ducts, we began to ask questions relative to lymphatics. Does the capillary filtrate, once it is in the lymph ducts, empty without loss into the venous circulation or is protein free to pass in and out of the lymphatic vessels throughout their lengths? Does any protein pass into the blood capillaries as the lymph traverses the lymph nodes and is in intimate contact with blood capillaries, or is any considerable amount of protein phagocytized by the reticulo-endothelial cells of the lymph nodes? Furthermore, to what degree, if any, is the lymph shunted to the blood stream through lymph-blood vascular anastamoses other than the thoracic duct? Anomolous shunts, consisting of multiple outlets of the right and left ducts, have been described (7) as well as shunts between the right and left thoracic ducts in about 15% of dogs (18). Several years ago, we set about answering

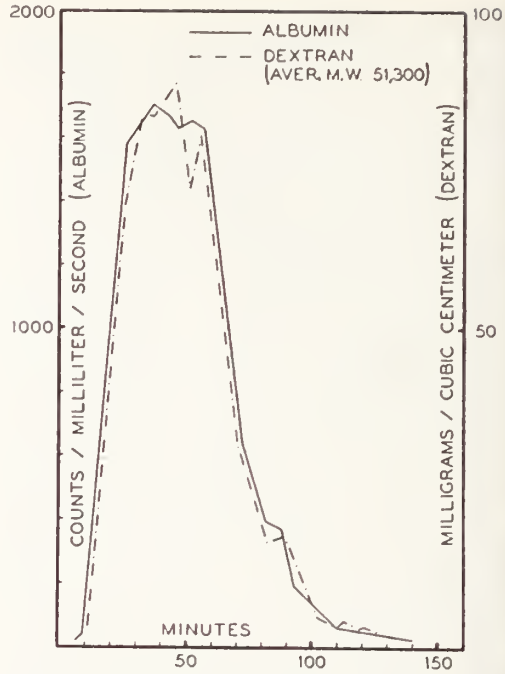


FIG. 9. Concentrations of dextran (average M.W. 51,300) and I^{131}-albumin in thoracic duct lymph. Mixture of I^{131} albumin and dextran infused centrally into leg lymphatic at zero time at rate of 0.5 ml./minute. Dextran and albumin infusion stopped after 50 minutes and 0.9% saline infusion started at same rate for next 100 minutes. Values for I^{131}-albumin are corrected for free I^{131}.

these questions in 2 more or less parallel studies, again with the help of medical students, Rodney Patterson, Allan McKee and my son, Peter. One study involves the cannulation of a leg lymphatic in the anesthetized dog, the infusion into it of substances of different molecular weights and obtaining and analyzing samples of thoracic duct lymph and plasma. We follow the same procedure as in previous studies of always including radioactive iodinated albumin in the infusions as a reference material. You will see the significance of this shortly.

The second approach to the problem was to utilize a preparation developed some years ago by Drinker and his group (29). One afferent and one efferent duct going to and from the popliteal node are isolated and catheterized with polyethylene tubing. All other lymphatics

are tied off. Test substances are infused through the node from the afferent side and collections are made on the efferent side. Nodal and systemic plasma are also obtained and analyzed.

When radioactive iodinated albumin is infused into a leg lymphatic, there is a typical, consistent pattern of appearance of the albumin in thoracic duct lymph (30) as shown in Figure 9. There is a lag time of approximately 10 minutes between the start of the infusion into the leg lymphatic and the appearance of measurable amounts of radioactive albumin in thoracic duct lymph. This is followed by an abrupt rise to a plateau which is maintained at an approximately constant level for the 50 minute duration of the albumin infusion and for 10 minutes of the subsequent saline infusion. At this time, radioactivity in thoracic duct lymph falls sharply and continues to fall until the level approximates zero in about 140–150 minutes. Plasma radioactivity rises to a maximum concentration after 60–90 minutes and remains at this level for the remainder of the experiment. The maximum plasma concentration is less than 0.001 of the thoracic duct lymph concentration during its 50 minute plateau period. Figure 9 also shows the similar behavior of dextran of approximately the same average molecular weight as albumin. It is apparent that these infused substances return to the circulation primarily by the thoracic duct. Actually less than 3 pc. of the infused material reaches the circulation by routes other than the thoracic duct except in unusual cases of right and left duct anastamoses. The experiments with the isolated lymph node preparation (31) suggest that most of the 3 pc. or less not recovered from the thoracic duct goes into the blood stream via the popliteal node and that there is little further loss in the other nodes through which the lymph passes on its way to the thoracic duct. We suspect that this is due to the fact that we are infusing under some pressure which is dissipated after the first node is passed.

We have tested a variety of substances of different molecular weights including the dextran fractions, radioactive sodium (Na^{22}), urea, sodium thiocyanate, glucose, cellobiose, raffinose and insulin. Briefly we have found that all of the macromolecules with molecular weight as large or larger than 6000, the molecular weight of insulin, are retained almost quantitatively in the lymph ducts and are returned to the venous system by the thoracic duct. I would emphasize that the test substance has traversed large and small lymphatics and a half-dozen lymph nodes in its passage to the thoracic duct and venous system. On the other hand, the smaller molecules like sodium, urea, etc. shuttle back and forth from the lymph ducts and equilibrate with plasma very rapidly. Recently we were fortunate in obtaining a dextran fraction of molecular weight of 2300. This substance seems to be borderline, small amounts (3 to 4 pc.) being found in plasma. The limits of permeability thus seem to be somewhere between approximately molecular weight 600, (molecular weight of raffinose = 594) and 2300. We shall try to close this gap eventually but are faced with the problem of finding suitable test materials since most of the substances available in this molecular weight range may form complexes of larger molecular weight when introduced into the lymphatic system and thus would give misleading data. Obviously we need to repeat these experiments in other sites. We are now repeating the infusions into a mesenteric lymphatic.

We ran into an interesting phenomenon quite by accident. In the early experiments with thiocyanate and urea, we infused high concentrations of materials so as to get sufficiently high levels in the plasma if the materials did get through. We found, as we had expected, that these low molecular weight substances rapidly equilibrated with plasma and only fractional amounts were recovered in thoracic duct lymph. However, these substances in high concentration obviously were injuring the lymphatic vessel walls since albumin was no longer retained in the usual fashion. Typical results are shown in Figure

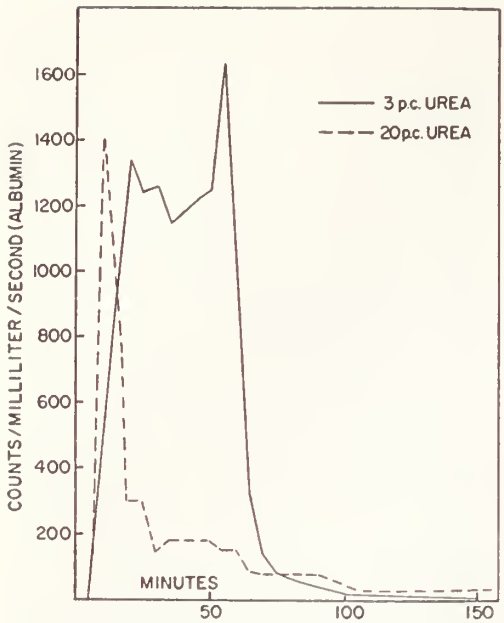


FIG. 10. Concentration of I^{131}-albumin in thoracic duct lymph. Mixture of I^{131}-albumin and urea infused centrally into leg lymphatic at zero time at rate of 0.5 ml./minute. Infusion of mixture stopped after 50 minutes and 0.9 p.c. saline infusion started at same rate for next 100 minutes. Values for I^{131}-albumin are corrected for free I^{131}.

10. When 20 pc. urea is infused, the albumin concentration rises quickly to a peak as before but now there is no maintained plateau. Instead, the concentration drops precipitously and remains low even though the infusion is still maintained. Also shown are the results of a 3 pc. urea solution. In this instance, the curve is more typical and there does not seem to be any injurious effect. There is also evidence of less edema around the infusion area. Similar results with evidence of injury were found with the experiments in which the urea infusion was made through the isolated node. Twenty to 30 pc. of the infused albumin was found in the tissue surrounding the node when concentrations above 5 pc. were used. Much more and other kinds of evidence are needed to establish the fact that high concentrations of urea are injurious to the lymphatics generally and perhaps to other tissues. The results, however, warrant caution in the use of high concentration urea solutions in clinical practice. We are continuing these experiments in the hope of answering some of the questions these experiments have raised. There still remains, of course, the most important problem of finding out the mechanism or mechanisms which control the entrance of macromolecules into the lymphatic system after they have leaked out of blood capillaries.

The final set of experiments I should like to mention concern kidney lymphatics and lymph. There has been much speculation but little definitive information as to their exact function (32). Do renal lymphatics act as a "safety valve" mechanism to protect the kidneys under conditions of diuresis or obstruction? Is hydronephrosis a dynamic insufficiency of lymph flow, in which excess fluid from the kidney cannot be carried off by the lymphatics? Is benign proteinuria of renal lymphatic origin? Does congestion of renal lymph vessels lead to interstitial edema in the kidney with a subsequent change in renal function? These and many other questions have been asked and only partial answers obtained. We therefore initiated a study of renal lymph several years ago. This has proved to be a very frustrating type of experiment. Lymphatics coursing along the capsule and with the blood vessels of the hilus are not difficult to find. The difficulty arises in their cannulation and in the collection of adequate amounts of lymph for analysis. With patience and perseverance we have been able to collect a reasonable amount of data on capsular lymph for the anesthetized dog under control conditions, during raised venous pressure, diuresis, ureteral obstruction and uranium poisoning. We were interested to discover that this renal capsular lymph contains protein in about half the concentration found in serum. The distribution of the proteins is similar (33). However, renal lymph has about a 10 pc. higher sodium concentration and about a 25 pc. higher chloride concentration. We need more data for these and other constituents and discussion of the significance of the above findings should, perhaps, wait until this data is available. I would, however, like to

TABLE 1

PER CENT INCREASE IN RENAL LYMPH FLOW AND COMPOSITION FOR MAXIMUM INFERIOR VENA CAVA PRESSURE (ABOVE CONTROL LEVEL) MAINTAINED IN EACH ANIMAL.

Dog No.	Inf. V.C. cm H_2O Press Elevated Above Control	Lymph Flow	Protein Flow	Na Flow	Cl Flow
		ml/min.	*gm/min.*	*meq/min.*	*meq/min.*
76	14	467	509	435	
71	16	200	150	206	92
74	18	700	698	501	306
75	20	400	153	346	
73	22	733	483	706	
72	30–35	900	2,218	875	689
69	35	1,025	4,961	1,017	1,181

briefly tell you the results of the experiments with raised venous pressure (34).

In these experiments we inserted a small balloon catheter into one femoral vein and positioned it in the inferior vena cava above the renal veins. A catheter was inserted into the second femoral vein and positioned below the balloon so that the inferior vena cava pressure could be recorded. Some of the results are shown in Table 1. Increasing the inferior vena cava pressure results in a significant and sustained rise in renal lymph flow which is generally directly related to the venous pressure increase. The rise in lymph flow is usually accompanied by proportionate changes in flow of electrolytes and proteins. This proportionality is lost, however, with respect to protein when the venous pressure is raised to levels of 30–35 cms. H_2O (dogs 69 and 72). Under these circumstances, there is a markedly disproportionate rise in renal lymph protein flow.

We have confirmed the findings of other investigators (35, 36) that elevation of the venous pressure results in a decrease in urine flow and urinary sodium concentration. There is general agreement that these changes can be explained on a mechanical basis although the factors concerned have not been clearly demonstrated. We suggest that the increased venous pressure results in raised tubular and interstitial pressure. This decreases flow in the loop of Henle and allows more time for sodium reabsorption with consequent greater water reabsorption in the distal tubule to bring the UP ratio back to unity. This results in a smaller amount of fluid flowing to the collecting ducts. Wirz (37) and Gottschalk and Mylle (38) showed that tubular fluid is isosmotic when it reaches the end of the distal tubule. The increased interstitial pressure around the collecting ducts and a decreased vasa recta flow may prevent loss of water from the collecting ducts and account for the reduced sodium concentration.

Our data may have some bearing on the problem of plasma volume increase and sodium retention in congestive heart failure, a syndrome in which venous pressure levels may approximate the high levels used in this study. As indicated in Table 1, high venous pressures may increase renal lymph flow as much as ten times when measured in one lymphatic. The average renal lymph flow during this period was 5.1 ml/hr. Our observations, as well as those of others, would suggest that there are at least 10 lymphatics draining the kidney. Under conditions of raised venous pressure, the renal lymph flow from one kidney may, therefore, approximate 50 ml per hour. The total lymph flow from both kidneys may therefore amount to as much as 2,400 ml per 24 hours. For a 15 kilogram dog this would be equivalent to 3 to 4 times the plasma volume and would represent a total of ± 35 meq of sodium not excreted by the kidneys but retained by the lymphatic system.

It may also be of interest to point out that under conditions of increased venous pressure, the lymph flow in one lymphatic may equal or exceed the urine flow through the ureter of the same kidney. Thus, in 5 experiments the average left ureter urine flow when the venous pressure was high averages 0.08 ml/min or 4.8 ml/hr. This is to be compared with the average renal lymph flow observed during the same period of 0.085 ml/min or 5.1 ml/hr. These results emphasize that although renal lymph flow may not be an important factor in the total fluid exchange under resting,

"normal" conditions, it may be an exceedingly important factor in "abnormal" situations. We are in the process of evaluating our data in the other experimental situations previously mentioned. If these results can be carried over to the human patient, they suggest that the effectiveness or ineffectiveness of the renal lymph system may be an important factor in the pathology of various types of renal disease. It may be pertinent to add that our results so far seem to support and strengthen the countercurrent hypothesis of renal function.

This, then, is where we have arrived at the present time. I have omitted the numerous side excursions into caves and bayous, excursions which were exciting and frequently profitable but which are separate stories. I have, by intention, limited my lecture almost exclusively to our own work. This does not mean disrespect or lack of admiration for the excellent work of other investigators. Our work has been done on the dog and there remains the question as to how many of our findings can be carried over to man. I do not have time to review the work on man but the evidence which is accumulating suggests that most of our findings and certainly all of our general concepts are valid for man. We do need, however, to know much more, not only about the role of the lymphatics in the healthy individual, but in the sick patient. As I emphasized at the beginning of my lecture, the primary function of the lymphatics, from a physiologic point of view, is to clear the interstitium of proteins, other macromolecules and substances which might upset the usual balance of forces on which homeostasis depends. It is a casual system, inherently dependent on activities of other tissues for the proper performance of its function. In this sense, it is a servant of the mammalian organism. It is usually a good servant, reliable, well-motivated and loyal and does a capable job when all is going well. When disturbances occur, it attempts to cope with them to the best of its ability. But its capacity is limited. As a phylogenetic late-comer, it was given a specific set of routine duties and it has not evolved to the point of being able to cope with more than routine stresses and strains. Again, like a good servant, it may get panicky in emergencies and in its zeal to help may actually make matters worse.

If you accept this concept that the lymphatic system is essential for homeostasis or "good health", I would urge you to give the lymphatic system the consideration it deserves in evaluation of disease states. In some instances, its role in the disease state may be quite obvious as a disturbance of its primary function. In others, it may be more difficult to discover the overlay of signs and symptoms resulting from an over-taxing of the lymphatic system. I feel certain that, as we learn more and more about the ramifications of its functions, this knowledge will be helpful in the diagnosis and perhaps eventually in the treatment of the patient.

REFERENCES

1. Starling, E. H.: The Mercers' Company Lectures on the fluids of the body, London: Constable, 1909.
2. Mann, J. D., F. D. Mann, and J. L. Bollman: Hypoprothrombinemia due to loss of intestinal lymph. Amer. J. Physiol. **158**, 311–314, 1949.
3. Bloom, B., I. L. Chaikoff, and W. O. Reinhardt: Intestinal lymph as pathway for transport of absorbed fatty acids of different chain lengths. Amer. J. Physiol. **166**, 451–455, 1951.
4. Linder, E. and R. Blomstrand: Technic for collection of thoracic duct lymph of man. Proc. Soc. Exp. Biol. and Med. **97**, 653–657, 1958.
5. Sabin, F.: A critical study of the evidence presented in several recent articles on development of the lymphatic system. Anat. Rec. **5**, 417–443, 1911.
6. Drinker, C. K. and J. M. Yoffey: Lymphatics, Lymph and Lymphoid Tissue, Cambridge: Harvard Univ. Press, 1941.

   Drinker, C. K.: Extravascular Protein and the Lymphatic System. Annals N. Y. Acad. Sciences, **46**, 807–821, 1946.
7. Yoffey, J. M. and F. C. Courtice: Lymphatics, Lymph and Lymphoid Tissue, Cambridge: Harvard Univ. Press, 1956.
8. Clark, J. H., W. Nelson, C. Lyons, H. S. Mayerson, and P. DeCamp: Chronic shock: problem of reduced blood volume in chronically ill patient, concept of chronic shock; hemoglobin and red blood cell deficits in chronic shock; quantita-

tive aspects of anemia associated with malignant tumors. Annals of Surg. **125**, 618–648, 1947.

9. Wasserman, K. and H. S. Mayerson: Exchange of albumin between plasma and lymph. Amer. J. Physiol. **165**, 15–26, 1951.
10. Masourides, S. P. and L. R. Melcher: Blood, plasma and "globulin" space of guinea pigs determined with I^{131} rabbit globulin. Proc. Soc. Exp. Biol. and Med. **78**, 264–266, 1951.
11. Wasserman, K. and H. S. Mayerson: Dynamics of lymph and plasma protein exchange. Cardiologia, **21**, 296–307, 1952.
12. Wasserman, K. and H. S. Mayerson: Mechanism of plasma protein changes following saline infusion. Amer. J. Physiol. **170**, 1–10, 1952.
13. Harroun, J. E., C. J. Smyth, and S. Levey: Tissue protein studies in normal and undernourished males: The changes in total circulation protein after an intravenous saline infusion as an index of protein stores. J. Clin. Invest. **29**, 212–217, 1950.
14. Calvin, D. B.: Changes in albumin: globulin ratios following intravenous saline injections. Amer. J. Physiol. **129**, 327–328, 1940.
15. Wasserman, K., L. Loeb, and H. S. Mayerson: Capillary permeability to macromolecules. Circ. Research, **3**, 594–603, 1955.
16. Pappenheimer, J. R.: Passage of molecules through capillary walls. Physiol. Rev. **33**, 387–423, 1953.
17. Grotte, G.: Passage of dextran molecules across blood-lymph barrier. Acta. chir. scadninav. Supp. #211, 1955.
18. Shirley, H. H., Jr., C. G. Wolfram, K. Wasserman, and H. S. Mayerson: Capillary permeability to macromolecules: stretched pore phenomenon. Amer. J. Physiol. **190**, 189–193, 1957.
19. Drinker, C. K.: Pulmonary Edema and Inflammation. Cambridge: Harvard Univ. Press, 1950.
20. Mayerson, H. S., C. G. Wolfram, H. H. Shirley, Jr., and K. Wasserman: Regional differences in capillary permeability. Amer. J. Physiol. **198**, 155–160, 1960.
21. Benson, J. A., Jr., K. S. Kim, and J. L. Bollman: Extravascular diffusion of protein. Amer. J. Physiol. **182**, 217–220, 1955.
22. Renkin, E. M.: Personal communication.
23. Brown, R. and J. F. Danielli: Active Transport and Secretion. New York: Acad. Press, 1954.
24. Hall, V. C.: Proc. 5th Annual Conf. on the Nephrotic Syndrome. New York: Nat. Nephrosis Found., 1953.
25. Pease, D. C.: Fine structures of the kidney seen by electron microscopy. J. Histochem. and Cytochem. **3**, 295–301, 1955.
26. Palade, G. E.: The Endoplasmic Reticulum. J. Biophys. and Biochem. Cytol. **2**, #4, suppl. 85–98, 1956.
27. Chambers, R. and B. W. Zweifach: Intercellular Cement and Capillary Permeability. Physiol. Rev. **27**, 436–463, 1947.
28. Moore, D. H. and H. Ruska: The fine structure of capillaries and small arteries. J. Biophys. and Biochem. Cytol. **3**, 457–462, 1957.
29. Drinker, C. K., M. E. Field, and H. K. Ward: The filtering capacity of lymph nodes. J. Exp. Med. **59**, 393–405, 1934.
30. Patterson, R. M., C. L. Ballard, K. Wasserman, and H. S. Mayerson: Lymphatic permeability to albumin. Amer. J. Physiol. **194**, 120–124, 1958.
31. Mayerson, P. and H. S. Mayerson: Unpublished observations.
32. Goodwin, W. E. and J. J. Kaufman: The renal lymphatics, I: review of some pertinent literature. Urological Survey **6**, 305–329, 1956.
33. LeBrie, S. J. and H. S. Mayerson: Composition of renal lymph and its significance. Proc. Soc. Exp. Biol. and Med. **100**, 378–380, 1959.
34. LeBrie, S. J. and H. S. Mayerson: Influence of elevated venous pressure on flow and composition of renal lymph. Amer. J. Physiol. **198**, 1037–1040, 1960.
35. Blake, W. D., R. Wegria, R. P. Keating, and H. P. Ward: Effect of increased renal venous pressure on renal function. Amer. J. Physiol. **157**, 1–13, 1949.
36. Hall, P. W. and E. E. Selkurt: Effects of partial graded venous obstruction on electrolyte clearance by the dog kidney. Amer. J. Physiol. **164**, 143–154, 1951.
37. Wirz, H. The Neurohypophysis, edited by H. Heller. New York: Acad. Press, 1957.
38. Gottschalk, C. W. and M. Mylle: Micropuncture study of the mammalian urinary concentration mechanism: evidence for the countercurrent hypothesis. Amer. J. Physiol. **196**, 927–936, 1959.

Philadelphia Doctors in the White House[1]

By DEAN ARVAN, M.D.[2]

IT IS a well known fact that Philadelphia has, from its earliest days, enjoyed the distinction of being in the limelight of medical progress. Contributions of Philadelphia's physicians have been monumental and pioneering. Their work in medical and allied sciences has been not only a great intellectual adventure, but also a prime contribution to the welfare of humanity.

It is also a well known fact that the severe illnesses of several Presidents of the United States through the years has had a dramatic and serious impact not only on the minds of the people, but on the state of the nation as a whole. Stirring up waves of emotion, agony, hopeful expectation and patriotism, causing political confusion and economic shake-up—all these serve as remarkable demonstrations of how much the hopes and aims of the United States and the world are linked to the man who occupies the American Presidency.

Ironically, many of these illnesses occurred during periods of considerable, and, at times, threatening political and economic turmoil, so that it was obvious to those concerned that the outcome of an illness could well mean the difference between national survival and disaster.

What is less known is the fact that Philadelphia's physicians, more than those from any other locus, have had leading roles in the management of such illnesses. A review of these roles is the purpose of my remarks. I will demonstrate how these men, at crucial moments, contributed their expert knowledge in the treatment of Chief Executives, and how, irrespective of the outcome, they proved to be outstanding men, exhibiting professional courage and moral judgment that was impervious to the heaviest of public and professional pressures.

Here, then, are four such illustrations in chronological sequence:

1) At 9:20 A.M., on July 2, 1881, President James A. Garfield was waiting at the Washington Station of the Baltimore and Potamac Railway, on his way to a class reunion at Williams College. He was accompanied by his personal secretary and several aides. Charles J. Guiteau, a malicious political hopeful, for reasons which were never clearly unveiled, approached the President from the rear and, coming within six feet of him, fired two shots from a .42 caliber revolver. One bullet went through Garfield's sleeve, but the fateful one struck him in the back. The President collapsed.

Dr. Willard Bliss was summoned immediately. On physical examination he found the point of entry of the bullet to be on the right side in the tenth inter-costal space, four inches from the mid-spine. There was a slight bloody discharge at the wound site.

Dr. Bliss passed a probe downward, forward, and to the left for 3½ inches to what appeared to be a cavity, but was unable to detect any fragments of broken ribs or the missile itself. Further repeated attempts at exploration also failed to recover the missile or give an accurate idea of its course and final location. It was presumed at this time that it was probably lodged in the liver. The President was taken to the White House in what appeared to be impending shock. He had repeated bouts of nausea and complained of pain and paresthesia in the legs.

At 7:00 P.M. on the same day, a consultation with other Washington and Army physicians was held and, after a thorough re-examination and exchange of views, it was decided that

[1] Edward Bell Krumbhaar Prize Essay III, Section on Medical History, College of Physicians of Philadelphia, 1960.

[2] Resident in Pathology, Hospital of the University of Pennsylvania, Philadelphia 4, Pa.

internal hemorrhage had occurred and that the patient would not survive the night. Much to their surprise, however, when morning arrived, the President was found to be alive and with approximately normal vital signs, good general appearance, and in an excellent mental state. It was at this point that Drs. Frank Hamilton of New York and David Hayes Agnew of Philadelphia were summoned for consultation regarding the mode of further treatment.

Dr. Agnew, upon arriving in Washington, examined the patient meticulously and, after a thorough analysis of all the available data, came to the conclusion that the patient should be treated conservatively because there were no clues that would indicate the approximate course or the final location of the bullet. Surgical exploration therefore appeared to be a dangerous and contra-indicated procedure.

Subsequently, the condition of the President remained quiescent until July 23rd, when he began having chills and a spiking temperature. Examination at this time revealed an infected wound and a chronically draining sinus. Between this date and September 19th, when he expired, he became progressively worse. A series of complications among which were parotitis, facial paralysis, otitis media, bronchopneumonia and frank staphylococcal septicemia led him to the final state of mental confusion and death. His terminal rectal temperature was 108.8 degrees.

A post-mortem examination revealed the following: 1) there was a fracture of the 11th rib; 2) the bullet had gone through the body of the first lumbar vertebra without affecting the spinal cord; 3) it had lodged in the retroperitoneal adipose tissue below the lower border of the pancreas, 2½ inches to the left of the spine; 4) there was a rent in the main trunk of the splenic artery, thought to have occurred about a week before death and to be of inflammatory origin.

Immediately following the President's death, there were sensational newspaper editorials analyzing the affair. Newspaper writers, anxious to boom the circulation of their journals, sharply and bitterly criticized the judgment of the doctors in charge. They seriously questioned the conclusion that the location of the bullet was undeterminable. Their main arguments were that the relative positions of the President and the assassin at the time of the shooting should have given enough clues, that a meticulous neurological examination might have pin-pointed the spinal cord injury, which caused the leg pain, and that an exploratory operation should have been done anyway.

Through all this storm, excitement, criticism and doubt, the small group of professional men maintained a dignified silence. In the sober light of after-judgment, it was eventually conceded by both lay and professional people that the President had been properly treated and that nothing had been left un-done.

Dr. D. Hayes Agnew, in these circumstances, once again displayed the personal and professional virtues for which he was so well known. Calm superiority of judgment, confidence in his diagnostic acumen, and a breadth of knowledge accumulated by his wide experience, formed a solidly-bound nucleus unyielding to popular clamor and extraneous pressures.

Dr. Agnew was born in 1818 in Lancaster County, Pennsylvania, and was educated at the University of Pennsylvania. At first a rural general practitioner, he found greater satisfaction in a combination of medical practice, teaching and experimentation, and so moved to Philadelphia, where he spent the most fruitful years of his life, ascending in time to the ranks of the medical élite. He was a capable surgeon and teacher of anatomy and surgery. One of the principal factors in his success was the Philadelphia School of Anatomy and Operative Surgery which he recreated and in which he refined the art of dissection and carried it over into surgical finesse. He was widely known as the clearest and most practical lecturer and demonstrator of his time, as a calm and ambidextrous operator, and as an expert on gun-shot wounds. He was a firm opponent to co-education of the sexes, and more specifically to medical educa-

tion of women. His career culminated in election to the Presidency of the College of Physicians of Philadelphia in 1888. He died in 1892 of cardiovascular-renal disease and diabetes mellitus.

2). The next episode concerned President Grover Cleveland and the fantastic operations performed upon him by Dr. W. W. Keen and other surgeons. Many years later, after he witnessed numerous speculative and newspaper accounts of the historical event, Dr. Keen decided to make public exactly what happened in those fateful days.

In order to understand the grave responsibility of Mr. Cleveland's surgeons and the absolute necessity of preserving tight-lipped secrecy, it is essential to have a clear cut picture of the financial disarray and panic that were then in progress—a period which has been described as the most intense financial and political storm in the history of our country.

The year was 1893. In the preceding few years several nations other than the United States gradually began demonetizing silver in favor of a gold standard. For reasons that only economists clearly understand, the United States was caught with a high surplus of silver and a rapidly decreasing gold reserve. To make matters worse, the Sherman Act, which was passed in 1889, imposed an additional 54 million ounces of silver yearly against which treasury notes were issued—all redeemable in gold. The end result was a tragic and confusing situation. Silver accumulated, the influx of gold ceased, bank failures occurred, trust companies closed their doors, and business embarrassments, even of large concerns, appeared in dismal reiteration.

Mr. Adlai Stevenson, then the Vice-President, was a pronounced "silver man". The President was not, and he intended to repeal the Sherman Act as soon as he could summon Congress. Obviously he was the only man who could save the country.

Such was the situation when on June 18, 1893, a 2½ cm. ulcer was discovered in the roof of the mouth of the President by one of the White House physicians. A biopsy performed immediately strongly suggested a malignant tumor. Dr. Joseph Bryant of New York was summoned and agreed with this diagnosis. He in turn called Dr. Keen of Philadelphia in consultation. Clinical evaluation revealed that the ulcer was of 6–8 weeks duration, that it had increased in size progressively, and that there was little discomfort from it. There was no lymphadenopathy and no other clinical findings.

It was decided that the President should be operated upon at once. Not only the life of the Chief Executive had to be saved, but the highest secrecy had to be maintained, for a political chaos would ensue should it become known that the chief silver antagonist harbored a serious disease. To accomplish the latter purpose, it was decided that the yacht of Commodore Benedict, a close friend of Mr. Cleveland, should be utilized for the procedure.

The living rooms of "Oneida", as the ship was named, were prepared and disinfected. An operating table was set up and instruments, drugs and dressings were put on board.

On July 1, the "Oneida" proceeded up the East River of New York, at half speed, after picking up its valuable cargo from some remote and deserted site on the East Coast. The entire procedure surpassed, in suspense, some of the best stories of foreign intrigue.

Two days later the dramatic operation was performed by Dr. Bryant assisted by Drs. Keen and John F. Erdmann of New York. Under nitrous oxide anesthesia, the two upper left bicuspid teeth were first extracted; next ether was substituted as anesthetic and the entire left upper jaw was removed from the first bicuspid to just beyond the last molar. The excision also included part of the soft palate. The maxillary antrum was found to be partly filled with a gelatinous mass thought to be a sarcoma. This diagnosis was later confirmed by Dr. William H. Welch of Johns Hopkins who had also examined the original biopsy specimens. (It has been impossible since then to firmly establish the diagnosis of malignancy, and to date there is considerable

doubt about it, since the President died fifteen years later of cardiovascular-renal disease without any evidence of local recurrence or metastasis. The surgical specimen removed and metal retractor used in the operation can be seen in the Mütter Museum of the College of Physicians of Philadelphia.)

In any event, on July 17th, a second operation was performed under identical circumstances to remove and cauterize any tissue that was left behind and appeared suspicious. Both operations were carried out intraorally, the floor of the orbit was not damaged, and the President was fitted with an artificial jaw made from vulcanized rubber.

The end result was that he returned to Washington without any external evidence of a scar and with no detectable affection of his speech. And so, in a special session of Congress on August 7th, the President urged the absolute and un-compromisable repeal of the Sherman Act, which was accomplished 2½ months later by the Senate, despite a fierce battle in which filibusters and wild accusations threatened to lead the country to disaster.

Thus, expert surgery accompanied by all possible pre-operative and post operative precautions, together with a dedicated follow-up and quick rehabilitation, served to dismiss the clouds of a storm and save a precious life in a dramatic episode of medical history in which the Philadelphian Dr. Keen was one of the protagonists.

Dr. William Williams Keen, though of small stature, was nevertheless a sturdy and vigorous man and had a very vivid personality. He exhibited his surgical skill early and he acquired much experience in the Union Army during the Civil War. His professional life was a very gratifying one. He was elevated to the professorship in several teaching institutions, retiring as Emeritus Professor of Surgery at the Jefferson Medical College. He was an excellent and popular teacher, a colorful writer and a bold and skillful operator. In 1887 he performed what is said to have been the first successful operation for an intracranial tumor in the United States, the patient surviving 30 years. He held the chair of the Presidency in several medical societies among which was the College of Physicians of Philadelphia. He also was a member of the National Research Council. He died in 1932, at the age of 95, after three years of invalidism from angina pectoris and a failing heart.

3) Dr. John A. Kolmer of Temple University described the next incident as the most touching and heart-rending experience of his long medical career. It concerns Calvin Coolidge, Jr., the younger son of President Coolidge. Dr. Kolmer tells the story as follows:

"In July, 1924, young Calvin sustained a minor abrasion on the middle toe of his right foot while playing tennis. The following day he complained of feeling ill, but the White House physician could find no evidence of specific disease."

"Two days later, he complained of pain in the right lower abdominal quadrant and developed some fever. Dr. John B. Deaver, another Philadelphian, was called in consultation with a provisional diagnosis of acute appendicitis. When examination revealed no genuine appendiceal pain, but instead slight right inguinal lymph node enlargement and tenderness, a local infection was suspected. This diagnosis became more probable when the abrasion was discovered on the toe, for young Calvin had made no previous complaints referable to it. A blood culture made the same day was positive for *Staphylococcus albus*, showing as many as 300 colonies per cc. There was a moderate coexistent leukocytosis."

At this time, Dr. Kolmer was called in, and, upon arriving three days after the original injury, found the boy in a stuporous state with the cardinal signs and symptoms of septicemia, although the abrasion of the toe showed remarkably little evidence of local inflammation. When deep tenderness was elicited over the right tibia, it was thought that there was an underlying osteomyelitis, which was probably the source of septic emboli. Dr. Deaver explored the region surgically, found no gross evidence of disease, although *Staphy-*

lococcus albus was again cultured from the bone marrow.

The patient, meanwhile, was treated with blood transfusions, soluble injections of mercurochrome and gentian violet (which at that time were still in the experimental stages) and anti-staphylococcal serum. On the sixth day of the illness, however, the patient lapsed into coma and it became evident that, despite heroic efforts, the outcome was hopeless. He expired just one week after the initial signs had developed.

President and Mrs. Coolidge were by the bedside in this 11th hour of cruel ordeal. It was during this time that the generally alleged cool and emotionless personality of President Coolidge revealed its true and heart-warming nature to those at hand.

Dr. Kolmer received doctorates in medicine and public health at the University of Pennsylvania, and later studied in Europe. His early staff affiliations were at the University of Pennsylvania. Dr. Kolmer became a widely recognized immunologist and bacteriologist, a persuasive teacher and an emphatic lecturer. I recall with admiration one of his lectures on syphilis, how he described with vivid dramatization the sneaky, silently-striking, pale spirochete, often spreading disease by overindulgences in what, otherwise, can be called natural acts, and causing syndromes with evasively protean manifestations, one of which is the euphoric state of syphilitic paresis. The Kolmer serodiagnostic test for syphilis immortalizes his name.

Dr. Kolmer describes the three most significant years of his career with a deep sense of respect and gratitude for those who contributed to his greatness. These were: in 1908, when, upon graduating from the University of Pennsylvania, he was awarded the Packard Prize in Medicine; in 1921, when he was appointed Professor of Bacteriology and Pathology at the Graduate School of Medicine at the University of Pennsylvania; and in 1932, when Dean Parkinson of Temple University School of Medicine invited him to become Professor and Head of the Department of Medicine. If medical degrees, scientific and public appointments, memberships in societies and fraternities, and number of publications are a good measure of a man's professional stature, Dr. Kolmer is a giant, for he has a colossal record of achievement in his lifetime.

4) Major General Howard M. Snyder was sleeping peacefully on the night of June 8th, 1956, when, around 11 P.M., the telephone rang. He picked up the receiver and the familiar voice of Mamie Eisenhower said at the other end: "Ike is turning and tossing in bed from a bad stomach ache. What should I do?" Knowing that his patient had a record of stomach complaints, Dr. Snyder prescribed some Milk of Magnesia and went back to sleep, only to be awakened again two hours later by another telephone call; this time Mamie said: "You better come over. Ike is getting worse." This the doctor did immediately. And so began a rapid turnover of dramatic events, which hit the population of the United States with tremendous impact for the second year in a row.

The operation on President Eisenhower for acute intestinal obstruction due to regional ileitis will be a milestone in the medical history of our country. At no other time was the public more precisely informed about a particular disease. Newspaper men recognized the fact that the life of the Chief Executive, even in its remotest details, is good publishing material. A serious illness can furnish exciting headlines and an endless number of news stories, so complete coverage is mandatory. To cite some examples of how far journalists will go, W.L. Lawrence, scientific editor of the *New York Times*, consulted the *Gould Dictionary* and the *Merck Manual*, and in a lead article gave a simplified but accurate description of the disease. Another correspondent discovered that Dr. Burrill B. Crohn, after whom the disease is named, was still alive, so reached him by telephone and this interview appeared in the same paper. Incidentally, Dr. Crohn was of the opinion that the President had the most common and safest type

of the disease, and the one most amenable to surgery.

The Philadelphia surgeon directly concerned with the case was, of course, Dr. Isidor S. Ravdin of the University of Pennsylvania School of Medicine. His first contact with presidential illness came a year or so before, when he was asked by the White House physicians to see a G-I series done on President Eisenhower during a routine examination. At this time an area of marked terminal ileal obstruction was discovered and the diagnosis of regional ileitis was established. Thus, when on Friday, June 9th, he received a telephone call from General Snyder concerning the events of the previous night, he knew precisely what had happened. At that time he was in Chicago, attending a meeting of the American College of Surgeons. He took the next plane to Washington. When he arrived there the President was already at the Walter Reed Hospital. The physicians present were: Dr. Leonard D. Heaton, who performed the operation; Dr. Ravdin, the chief surgical consultant; Dr. Paul D. White, consultant cardiologist from Boston; Dr. Snyder and Dr. Thomas W. Mattingly, chief cardiologist at the Hospital, who incidentally, was on his way home to South Carolina when his car was stopped by the State Police on the highway and he was taken to the nearest airport to be flown back to Washington in a jet plane, or so the story goes.

Meanwhile, things were moving fast and with military precision. The decision to operate came at a mid-night medical conference, almost twenty-four tense and confusing hours after the initial symptoms developed. At this time the patient was not any worse, but the obstruction showed no signs of regression, and there was still considerable vomiting and abdominal pain.

Within two hours the President was in the operating room. I could not describe the procedure better than TIME magazine did in its June 18 issue of that year: "In operating room six of Walter Reed Hospital a massive bowl-shaped lamp bathed the operating table in its shadowless glare. Bending over the table with hawk-like attentiveness were the four surgeons in their blue-green gowns, with skull-caps and masks, tersely and softly directing a team of twenty physicians, nurses and technicians. On the table, his breathing regular as he fell into a deep sleep, lay Dwight D. Eisenhower, 65, 34th President of the United States, undergoing major surgery to relieve obstruction of the small intestine. Nearly two hours later, with a steel-gray dawn just breaking over Washington, came the announcement that the operation had been a success."

Naturally, the first question the newsmen asked afterward was: "Will he be able to run again?" The first thing the President said, when he came out of the anesthesia, was: "What a belly-ache!" And indeed it was, not only for him, but for the entire nation.

The operation lasted one hour and 53 minutes. There is some disagreement among the chief surgeons as to the actual pathology found. Dr. Heaton explained to the reporters the next day at a special conference that ten inches of terminal ilium was found to be markedly contracted, inflamed, and with the consistency of hard rubber hose. But Dr. Ravdin questions the evidence of acute inflammation. He claims that the President was operated upon for simple intestinal obstruction. Be that as it may, an ilio-transverse colostomy, rather than a resection, was performed for the following reasons: a) acute recurrence of the disease rarely occurs at this age; b) the longer procedure of a resection would probably be contra-indicated for a patient who had acute coronary occlusion only one year before; c) a by-pass would probably be just as good for a disease that was fairly localized.

Up to date, Dr. Ravdin has been proven to have used excellent judgment. The President not only survived the operation but made a remarkably speedy recovery. Just 31 hours post operatively, in accordance with the concept of early ambulation, he was walking with assistance. The remainder of his convalescence was completely uneventful.

It is evident that the life of the Chief Executive is anything but a private one, and, that anything that threatens his well-being has an appalling effect on the general public.

Dr. Isidor S. Ravdin, John Rhea Barton Professor of Surgery at the University of Pennsylvania, needs no introduction, for his fame is of international dimensions. He received his medical education at the University of Pennsylvania, graduating in 1917, and has directed the Harrison Laboratory of Surgical Research from which have come many fundamental contributions to surgery. He is a Major General Retired, U. S. Army, and was decorated with the Legion of Merit during World War II. He is a member of the National Advisory Cancer Council, Alternate Member of the Civil Advisory Council to the Secretary of Defense, and Senior Civilian Consultant to the Surgeon General of the Army.

The above examples by no means exhaust the list of distinguished Philadelphia physicians who served occupants of the White House. Other examples from Philadelphia's medical circles could be cited who offered their talented professional advice in the diagnosis and management of presidential illnesses. Some spent only a portion of their illustrious careers in Philadelphia, so I am not sure it would be correct to make a claim on them. Others played only a minor or consultative role. To mention a few of the better known: a) Dr. Robley Dunglison, who spent the last thirty-three years of his career at Jefferson Medical College, was personal physician to President Thomas Jefferson and treated him for, among other things, prostatic hypertrophy and urethral obstruction. He also participated in the management of President James Madison's "rheumatic affection", and President Andrew Jackson's "pleurodyne"; b) Dr. Jacob Mendez Da Costa of Jefferson Medical College was called in consultation to treat President Ulysses S. Grant when the latter was suffering from carcinoma of the tongue and tonsil; c) Francis X. Dercum, internist-neurologist at the University of Pennsylvania, and later at Jefferson Medical College, and Dr. George E. de Schweinitz, noted Philadelphia ophthalmologist, were called to see President Woodrow Wilson, who, on October 2, 1919, suffered a cerebrovascular accident with left hemiplegia; d) Dr. William Williams Keen, then at the peak of his fame, and while vacationing at Bar Harbor, was one of the first to be called to examine Franklin D. Roosevelt, who, in 1921, developed the signs and symptoms of an upper respiratory infection and then paralysis of the legs later proven to be paralytic poliomyelitis.

In conclusion, I wish to re-state the fact that few cities have produced so many medical experts, who, during turbulent and dark moments of national history, have been called upon to render professional service to the Presidential occupants of the White House.

Acknowledgment: The author acknowledges the assistance of Drs. Charles S. Cameron, Hahnemann Medical College, Samuel X Radbill, University of Pennsylvania Graduate School of Medicine, and Fred B. Rogers, Temple University School of Medicine.

REFERENCES

1. Adams, J. H.: *History of the Life of D. Hayes Agnew, M.D., LL.D.*, Philadelphia, F. A. Davis Co., 1892.
2. White, J. W.: *Memoir of D. Hayes Agnew*, Trans. Coll. Phys. Phila. **15**, 29–65, 1893.
3. Keen, W. W.: *Surgical Operations on President Cleveland in* 1893, *Together with Six Additional Papers of Reminiscences*, Philadelphia, J. B. Lippincott, 1928.
4. Wold, K. C.: *Mr. President, How is your Health?*, St. Paul, Minnesota, Bruce Publishing Company, 1948.
5. Kolmer, J. A.: *The Fatal Illness of Calvin Coolidge, Jr.*, Temple University Medical Center Bulletin, vol. 1, no. 4, pp. 7–8, April 1955.
6. Kolmer, J. A.: *My Three Greatest Years in Medicine*, Temple University Medical Center Bulletin, vol. 2, no. 4, pp. 8–9, April 1956.
7. Kolmer, J. A.: Personal Communication.
8. Ravdin, I. S.: Personal Communication.
9. Life Magazine, June 18, 1956
10. Time Magazine, June 18, 1956.
11. New York Times, June 10–11, 1956.
12. Radbill, S. X.: *Robley Dunglison, M.D.*, 1798–1869: *American Medical Educator*, Jour. Med. Education **34**, 84–94, Feb. 1959.

Observations of a Pilot "Health Education Center" in a New-Immigrant Town in the Upper Galilee[1]

By NAOMI R. BLUESTONE, B.A.[2]

THE small Israeli town of Qiryat Shmona lies in the valley between the mountains of Lebanon and Syria. It is a sprawling collection of housing developments, schools and small shopping centers built along the mountainside. Qiryat Shmona is a peculiarly Israeli phenomenon . . . a town which sprang up literally overnight, peopled with new immigrants to the country whose greatest common bond was the need to be settled quickly, in as normal a living situation as possible. Ten years ago it consisted of 300 people living in Arab huts; today it is a boom town of 14,000 residents, most of whom have been in the country for only a few years. These new *"Olim"*, as they are called, come from more than 30 different countries, but most of them are from North Africa and Israel's surrounding Arab states.

The new Olim here are nick-named "the primitive ones", not unkindly, and so indeed they are. Educating them to take their place as responsible citizens in a 20th century mechanized democratic state is truly a massive undertaking. The most basic discipline they must acquire, the foundation of all subsequent adjustments in thought, culture and strength, is thorough grounding in their education toward health. The people of Israel recognize that a people scourged by trachoma, tuberculosis, malnutrition and high infant-maternal mortality, with all the other attendant afflictions of ignorance and backwardness, will never be able to aid the growth of a new nation. It is for these people, nurtured in poverty, ignorance and gross sociological affliction, that a pioneering program in health education has been set up by the Ministry of Health of the Israeli Government.

The agency charged with this rather awesome task is housed in a friendly-looking building, in appearance not unlike the recreation hall in a summer camp. This is the "Mercaz Ha-briut" (Health Center) whose modest exterior belies the extensive work it is doing in this part of the northern Galilee. Its facilities include a comfortable meeting room, with an expanding medical library which includes all the leading international journals of public health; a "maternity suite" for midwife deliveries of the town babies (with accommodations for after-care for ten mothers); offices for the Center's Business manager, Chief nurse, Medical Director, and Director of Health Education; a kitchen which serves regular meals to staff and guests; and small rooms and nurseries for well-baby clinics, as well as some limited clinical facilities.

Three key health workers control the Center's activities. The Medical Director of the center, Dr. Salomonovitch, a European-trained gynecologist, supervises four young midwives. The Chief Nurse, Mrs. Rachel Weinshank, is a native Israeli, who coordinates the activities of ten Public Health Nurses. The third member of the team, Mr. Shalom Levi, is the only full-time health educator in the country. An office and custodial crew, under the supervision of the Business manager completes the staff.

The Mercaz, as opposed to health offices in other cities, makes no attempt to control civic

[1] William Harvey Perkins Prize Essay II, Section on Public Health, Preventive and Industrial Medicine, College of Physicians of Philadelphia, 1960.

[2] Third year student, Woman's Medical College of Pennsylvania. This study was done during the summer of 1960 under the sponsorship of the American Friends of the Hebrew University.

sanitation facilities, such as water inspection, garbage and sewage disposal, anti-malaria crews, etc. The services which it does supply will be briefly outlined, and an attempt made to show how they are approached from point of view of specific education towards health.

MATERNITY SERVICES

Services at the Mercaz begin with the new-born citizen, whose home is completely unsuitable for his delivery, and whose mother cannot usually negotiate the one to two hour (expensive) trip to the hospital in Safed or Poria. In the four years of the center's work, there have been 2,000 deliveries with only one maternal death. Mothers whose first few children were born in the "old country", are given the privilege of a 20th century birth, gleaming and sterile.

After comprehensive prenatal care, the Medical Director carefully screens mothers among whom complications may be anticipated and these women are sent to the hospital for delivery. Normal births, however, are frequently accomplished by the midwives alone. Following a night delivery by a midwife, the M.D. receives a report, examines the placenta, and does routine blood studies (average hemoglobin: 8–10 grams) when he examines the patient.

A normal birth at the Mercaz is a highly informal affair, easily accomplished without instruments, anaesthetic or undue excitement. It is characterized by a fine working relationship between midwife and mother, in which apprehension is minimal and cooperation active. There is a rooming-in program for the baby, who is always at his mother's side. Visiting hours are also uncurtailed, and older brothers and sisters are constantly peeking in the porch windows and running underfoot. It is the firm belief of the Medical Director that this liberal policy is well worth the increased bacterial count, in terms of encouraging public trust in the Center, and in increasing the closeness of the family with the new baby. (This policy, by the way, is a warmly disputed topic when foreign visitors come to the Center.)

The length of stay of the new mother depends upon her physical condition and the situation at home; despite the luxury of rest, quiet and hot water (all paid for by her insurance program), she is usually anxious to be off in four or five days. Before she leaves, however, she is taught how to care for the baby, how to care for herself, and therefore, how to better care for the other children at home.

MOTHER-CHILD CLINICS

A Mother-child Clinic is the next important step in the services of the Mercaz. Still called colloquially "*Tipat Chalav*" (which means literally, "a drop of milk") this clinic is one of many across the country designed to teach participants the most fundamental aspects of diet, sanitation, and baby care.

Gaily decorated picture placards on the walls demonstrate the value of drinking milk and brushing teeth. The green clad public health nurse is ready to discuss any problems with the new mother, and these are as variable as the background from which she comes. Before a new immigrant can be taught the importance of weekly weighings for her baby, she must be taught what a scale *is*, and what the numbers mean, and the significance of the concept "kilogram". It is here that prenatal instructions are re-inforced, and the counsels of the old grandmother fortunately tempered with modern attitudes. Opportunity is afforded to chat with other new mothers and a highly sociable atmosphere accompanies the weekly weighing-in.

The new baby's birth must be properly recorded. (A significant percentage of modern Israel still must confess that "I am about 33 or 34 years old" because records were considered unessential in the old country). The regular weighing and measuring at the clinic is important both for the child and for the Health Department's statistics. With a massive ten-year influx of Jews from every country of the world, Israel is faced with the problems of establishing norms in body growth. Spock's growth curve for a blonde blue-eyed baby in Boston is valueless against a tiny black-eyed

Yemenite baby in Qiryat Shmona. No one yet knows how tall, how wide, how heavy an oriental youngster should be.

At the mother-child clinic, there are the usual activities of supervision of diet and basic immunization procedures. Sick children are referred to physicians. And as all this is being done, the public health nurse is establishing rapport with the heart of her community—the individual family.

PUBLIC HEALTH NURSE

As the child grows up, he and his entire family are assigned to the Public Health Nurse who covers his section of the town. Services which the American Public School Nurse performs in the classroom are taken care of in the individual home, for the keynote of the Mercaz philosophy is its *family-centered* care. (The work of the Public Health Nurse in the schools is directed toward education of the teacher to the health problems of her children, so that she may be a well-informed partner in the care of the child.)

The public health nurse is a common sight on the rocky roads of Qiryat Shmona. She wears a green dress with white collar, sturdy oxfords and bobby socks . . . and usually a floppy straw hat to shield her from the merciless Middle East sun. She is usually a young girl who has completed two or three years training at a school in one of the large cities. She has been sent by the government for at least one year's service in a border settlement or new immigrant village, and she is admittedly unhappy to be stuck away in this "hick-town." However, her patriotism is strong, and she is usually good-humored about the whole business; morale among the young nurses in Qiryat Shmona is refreshingly high.

Because very few people in the town have telephones, she must trudge, frequently from one end of the town to the other, to visit patients—who may well be out when she arrives. If they are home, she is joyously welcomed.

The Public Health Nurse's task is to teach. Each time a baby is bathed in a basin on the cot bed, and emerges a scrubbed contrast to the encrustations of filth all around him the mother receives another lesson on how things are done in the 20th century. After a few visits, the mother will learn to bathe the baby herself. Then the oldest girl will bathe the baby. And then there will be a new baby to bathe. If the mother is quick and eager to learn, as indeed most of them are, she soon sees that as clean as her new baby is, so must she be herself, and that the birthright of cleanliness is not to be given up when the baby is old enough to crawl and get himself *really* dirty. The courtesy of cleanliness must be extended to his clothes and his bed and his food . . . but a mother who has been herself accustomed to living more like an animal than a human being can not learn all this at once . . . so the public health nurse goes on to another family, carefully controlling both temper and sense of humor.

VISITING SPECIALISTS

While the nurse is making her rounds, the Mercaz is open for business in the form of one of its best attended services, the visiting medical specialist. Doctors from hospitals in the neighboring cities set aside a day of the week to come to Qiryat Shmona. An X-ray and photofluorographic service is extended for mass screening procedures; also dental services, eye and ear examinations and, as of next month, pediatric consultation . . . although the Mercaz refuses to consider itself a medical organization and claims these are merely preventive medical services. Each day, then, brings the townsfolk in to the Mercaz, and they sit patiently, if noisily, until called. Squatting on benches, sitting on the floor, chattering in Arabic or Persian or Hebrew, they present a colorful picture to the visitor.

AFFILIATED SERVICES

The Mercaz is not the only medical organization in the town, and indeed it's two closest neighbors must of necessity work with it hand in hand. One of these is the Kupat Cholim (Sick Fund) of the Worker's Union, where

actual medical treatment is carried out; the other is the local new station of the Mogen David Adom, the Israeli counterpart of the American Red Cross. Phones between the three organizations are buzzing constantly, and favors and requisitions are granted liberally. All the services of the Mercaz are extended to members of the numerous kibbutzim (collective farming settlements) which dot the area, and some special programs are geared specifically for them.

PROFESSIONAL EDUCATION

The Mercaz, believing that teaching people to help themselves is the best method of achievement for the future, offers a program of adult education for the townspeople, the "kibbutzniks" and its own staff. Seminars are held on infectious diseases such as polio, on old age problems, chronic diseases, etc., and invited to attend are medical personnel from the neighboring cities of Tiberias, Safed, Afula, Acre and Nazareth. A successful innovation has been the joint participation of doctors and nurses in one class on epidemiologic methods.

The Mercaz has recently cooperated in a 60-hour course in Red Cross First-Aid to recruit volunteers from the town to man the newly-opened station. The Medical Director of the Mercaz who also directs the first-aid station, and the Director of Health Education are two of the instructors of this course; participants included members of the nursing and office staffs.

Another well-attended institution is the weekly or bi-monthly class for food-handlers in the surrounding kibbutzim, which may draw up to 25 dungaree-clad workers on an afternoon. They participate in lively discussions concerning their mutual problems of refrigeration, sterilization, inspections, etc. The visiting lecturer may be a sanitary engineer from Jerusalem, or one of the class, who has licked a particularly nasty problem in his own kibbutz.

The highly specific health problems of these farming settlements are of particular concern to Mr. Shalom Levi, who is himself a member of one of them. Much to the regret of the Health Department, these pioneering folk who, with fearless disregard of life and limb, drained the malarial swamps when the country was still desolate, have not proved as amenable to suggestion as the new immigrants. They are a stubborn lot who have endured so many years of deprivation and sacrifice, they feel they cannot be "bothered" with health education. It is their great tradition to ignore sickness and personal suffering, and they feel it almost "sissy" to worry about washing their hands before a meal. Mr. Levi, in his capacity as Health Educator serves as a connecting link between the 20th century Health Department and the pioneer settler; he is devoting much of his time to the resolution of these misunderstandings. Realization that these problems do exist has been the first step forward in the eradication of current evils in the communal dining room: barefoot waiters, lack of screening against hordes of flies from nearby barns, unbelievable noise and confusion, constant turn-over in kitchen personnel and, in general, an almost total disregard for the basic elements of sanitation and good eating habits.

INFORMATION CENTER

In addition to its function as a center of some educational activity, the Mercaz is also an important source of information on a community, national, and even international basis.

Within the town, the doors of the Mercaz are always open; the people know that in time of trouble, emergency or doubt, they will receive proper instruction and information at the brown building. This willingness to deal with all problems has transformed the center into a veritable Community Center, a position it views with welcome—but at times, a little dismay.

On a wider scale, officials of the Ministry of Health in Jerusalem depend upon the Mercaz for vital information concerning the health situation in this part of the northern Galilee. Reports from the "backwoods" enable the central office to plan better lines of attack in

prevention of disease in the whole country. The Mercaz also serves as a source of information for visitors from all over Israel and from foreign countries.

The staff of the agency is especially happy to discuss with representatives from new small countries mutual problems and comparative methods of solving them. Much valuable exchange of information is effected in this way, and a steady stream of new innovations results from these informal chats over morning lemonade and cookies.

FOCUS OF MEDICAL THOUGHT AND RESEARCH

The workers of Qiryat Shmona consider it important to keep themselves in touch with the latest trends in modern medicine and are eager to make their own contributions along that line. At present they are participating in a project using a new live oral polio vaccine which is given to new babies after they leave the Mercaz.

The Mercaz is also participating in a nationwide research project on rheumatic fever, to determine incidence and prevalence of the disease in the country, as well as possible methods of eradication. This work is not confined to the limits of the town, but is extended into the kibbutzim, thus enabling comparison of the rural with the urban situation. Advantage has been taken of the excellent controls the kibbutz offers for this sort of study; i.e., the children all live together, four to a room, in the Children's House, eat the same meals, and, in general, share the same socio-economic status. (The kibbutz is indeed a "ready-made laboratory" for anyone who wishes to conduct a study in which control of socio-economic factors is of prime importance.)

For aid in this type of work, the Mercaz enlists the assistance of the kibbutz doctor, who is a willing aid to communal workers. These physicians are for the most part epidemiologically oriented, and can contribute accurate statistical data. More than one has been eager to prove (and this has been done) that a general country practitioner can turn in a major piece of research, despite his isolation from the research facilities of the Medical School of the Hebrew University in Jerusalem.

MEMBER OF THE TEAM

Although its program is unique from the standpoint of health *education*, the center in Qiryat Shmona is but one of many scattered throughout the country. Israel is sprinkled with government-sponsored visiting nurse substations and mother-child clinics, some of which function in conjunction with the health centers of sizeable cities, others of which are scattered in way places. Qiryat Shmona cooperates with these other health centers throughout Israel, which are all linked under the national program. Qiryat Shmona falls within the Northern District of the country, which includes Safed, Tiberias, Afula, Acre, and Nazareth, and the farmland and arab villages in between. It is in constant communication with these other offices of the Department of Health, and it participates in common programs as another member of the government team.

THE GREATER ROLE

Both the theoretical forces behind the center and the practical forces within recognize that there is no substitute for teaching by precept. For this reason, the personal lives of the personnel are firmly integrated into the town. The "*Vatikim*", or old-timers, who man the Mercaz, serve as a central core of citizenry for the new town, and live within the housing developments. They are active in civic affairs; they promote legislation that is enlightened to the problems of the community; they become good neighbors. And in turn, the center gives them a rallying point of encouragement, when they feel stranded in a wilderness of "primitive ones" and long to escape back to the more civilized cities.

The final and certainly the most important aspect of the work of the new Health Center, then, is its role as a uniting, cohesive force in the assimilation of people of various cultures in *all* ways of life. Its work in reality far transcends the humbler tasks of health educa-

tion, which becomes a means to a greater end, and just a small part of the responsibility of the State to build one nation of disparate groups of settlers.

SUMMARY

In all of the above undertakings, the policy of the agency has been care structured about the individual family unit, with accent upon teaching the individual to do for himself. This is accomplished by means of excellent teamwork; high staff morale and sense of purpose; free and unstrained supervisor-personnel relations and coordinated interaction of the various services. The feeling tone of the agency is optimistic and busy with typically Israeli "first-name" informality operating at all levels.

It should be noted that life for many reasons is of necessity slower-pitched than rural life in America. Despite a 20th century office (*early* 20th century) telephone service is very slow, three hours frequently being necessary for a routine call to Jerusalem, somewhat less to Tel-Aviv or Haifa. Public transportation is uncertain; private transportation expensive and all too often, non-available. The hot climate precludes too much mid-day strenuous activity, also. But despite the myriad inconveniences encountered by the push-button American, progress continues steadily, and the center continues to play more and more important a role in the lives of the townspeople.

What have been the objective accomplishments of the center?

After four years, the Mercaz has made substantial inroads into conditions of mass poverty, ignorance, fear, misunderstanding and seemingly hopeless backwardness. The basic fundamentals of hygiene and sanitation have been pounded into the heads of the salvageable young leaders of the family. The people have learned to turn to the center for guidance, for care, for material help with innumerable problems of daily living in this new, free country. The center has experimented, remained flexible, learned ever increasingly new techniques in methods of education and service to a community totalling 25,100 people. They have proven themselves invaluable to the town and pioneered a new concept in the Health Center Program, demonstrating that an agency geared primarily to education is the answer to teaching people to help themselves. Superstitions and belief in primitive methods of medical care are being steadily swept away and replaced by faith in Israeli physicians. (No less remarkable is the fact that the center has not alienated the people whom it is trying to help by any lack of understanding of their customs.)

Health workers at the agency frequently confess to feeling overwhelmed, inadequate, and even unsure quite what it is they are trying to accomplish. Having no precedent to follow, they are experiencing all the problems of an agency with a new purpose. Their projected goal for the future is to maintain their progress to date, a progress which they feel to be almost "too good to be true", and to find better methods of organization and follow-through of activities.

Their success seems assured.

Community Health Interests of Temple University Medical Center*

By VICTOR J. LoCICERO, M.D., AND WILLIAM A. STEIGER, M.D.

ON MAY 18, 1960, the Pennsylvania Public Health Association and Section on Public Health, College of Physicians of Philadelphia, sponsored a panel discussion on "Social and Emotional Factors in Urban Illness". William A. Steiger, M.D.[1] was moderator, and panel members were Francis H. Hoffman, M.D.,[2] Victor J. LoCicero, M.D.,[3] James F. Rooney, M.S.W.,[4] and Miss Sheila Scott, R.N.[5] The panel theme and the professional affiliations of the members are indicative of the growing trend in medicine to give recognition to the myriad factors involved in the understanding and treatment of human illness. This is expressed by uniting with workers of other disciplines for the common purpose of better understanding and more effective treatment of human problems. This trend is especially seen in Psychiatry with its growing involvement in community problems. Among the interests of Social Psychiatry are the treatment of lower socio-economic groups and the major public health problem of alcoholism.

Dr. Steiger first described the efforts of the Comprehensive Medicine Clinic in dealing with one of the community problems, the physical and mental health of lower socio-economic groups. He stressed the comprehensive medical approach which insures the recognition and consideration of the interplay of the biological, psychological, and sociological forces and their implications for treatment. Dr. Steiger then briefly described the follow-up study of medical clinic patients which has been in operation for almost two years. One of the findings has been the isolation of a clinic subculture, termed the "young male syndrome". This refers to a male under 50 years of age who appears for medical help at this medical clinic. Often he is either psychotic or bordering on a psychosis. He either does not return after the first visit, or comes two or three times. Near completion, this follow-up study is expected to yield information dealing with the results of treatment, an analysis of the types of problems and the population treated, and some leads to the operational factors in successful and unsuccessful results.

The general theme of community problems was expanded by Dr. Hoffman who told of the Psychiatry Department's interest in this area which led to the formation of the Division of Social Psychiatry. Two problems currently being examined by this unit are the rehabilitation of the alcoholic inmate at the House of Correction, and the study of the Philadelphia Skid Row prior to redevelopment of that area. The House of Correction project is unique in that the combined efforts of a University Medical Center with all its resources and a correctional institution are being utilized to tackle a community problem. With recognition of the complexity of the problems undertaken, an interdisciplinary team was organized. This team consists of psychiatrists, psychologists, sociologists and social workers. Consultants to the team include specialists in such areas as vocational rehabilitation, criminology, economics, and hypnosis.

The efforts of the team were discussed by

* Report of a panel discussion arranged by the Pennsylvania Public Health Association, and Section on Public Health, College of Physicians of Philadelphia, and held at Lankenau Hospital in Philadelphia.

[1] Director, Comprehensive Medicine Clinic, Temple University Medical Center, Philadelphia 40, Pa.

[2] Co-Director, Comprehensive Medicine Clinic, and Director of Resident Training, Department of Psychiatry.

[3] Director, Interdisciplinary Unit in Social Psychiatry.

[4] Research Worker in Sociology, Division of Social Psychiatry.

[5] Research and Clinical Assistant, Division of Social Psychiatry.

Dr. LoCicero who began by considering the salient characteristics of the average alcoholic inmate. He is usually a man of 40–45 years of age who feels lonely and isolated, and has withdrawn from close interpersonal relations. Strong dependency problems are manifested in feelings of helplessness in the face of small obstacles handled routinely by the average adult. He is chronically depressed and angry. There is a sense of futility, boredom, self-reproach and sadness. Most often his anger is not expressed or recognized by him, hence, he is a peaceful man who may become belligerent only when intoxicated. Sexual problems are present in varying degrees and are reflected in feelings of inadequacy as a man. In his background there is much emotional trauma and desperation. He is lacking in every possible way; there is a deficiency in social and occupational skills, in education and in health. Known to be difficult to treat and lacking systematized data to serve as a guide, the problem of the "revolving door" alcoholic was therefore approached in an exploratory manner. The chronic alcoholic offender was likened to the chronically regressive psychotic in the back wards of state hospitals. Until quite recently the same helplessness and feeling of futility existed regarding treatment. Taking into account such difficulties, a rehabilitation program was organized based on the premise that to be even slightly successful, help in all areas of deficiency would be necessary. The program provides help with obtaining jobs, food and clothing and shelter. In addition it includes group and individual psychotherapy, drugs, and work with other family members when present. Rehabilitation starts in the House of Correction and continues after discharge. Numerous community agencies cooperate in the treatment program. These include Department of Public Assistance, State Employment Service, religious groups, and private social agencies such as the Prisoners Welfare Aid Society and Goodwill Industries. A persistent problem has been the lack of facilities in Philadelphia for the treatment of the indigent acute alcoholic requiring in-patient care. As might be expected, many cannot quickly achieve sobriety. Those who resume drinking and return for help, very often cannot be provided with suitable treatment. Hence, they gravitate to Skid Row and eventually are returned to the House of Correction, unable to free themselves from the forces of the "revolving door". The lack of a facility, such as a "halfway house" which could provide continued treatment after discharge and until the individual can maintain himself, is felt to be a definite handicap.

In the search for greater understanding and for effective treatment of the problem, a number of studies are being carried out. These include a sociological study of the House of Correction, follow-up studies, the effect of alcohol on various drives, such as aggressiveness and hostility, study of the children of alcoholics, and the use of hypnosis as a form of treatment. In addition, group therapy is being studied with particular emphasis on dependency problems, the relationship between the therapist and the patient and problems of moderation for group therapy. As indicated in the Hollingshead and Redlich Study, "Social Class and Mental Illness", problems in the psychological treatment of the lower socioeconomic groups exist. These may be in the area of communication across class barriers and value differences. Our findings may then be compared with this study. In this respect, the findings of the Medical Clinic follow-up study will have similar implications. The Skid Row study, although having its primary focus in problems of redevelopment, is also expected to yield other helpful data. The first phase, a census of the Skid Row population, has been completed, and the data is being analyzed. Phase II, an intensive sociomedical study of a sample of this population is expected to start soon. Since the follow-up study of inmates who participated in the rehabilitation program is not yet completed, only impressions in the form of anecdotal material can be given at this time. Some participants show trends toward improvement. An identification with the program and the community is noted. Friends are referred for help and help is offered with the program. There are feelings of greater responsi-

bility; one individual repaid some of the money loaned him, stating that this was the first time in his life he had repaid a debt. Members help with locating other group members and bring them to meetings. Alleviation of depressed feelings is also seen. One member said this was the first time in 15 years he felt happier and optimistic, realizing at the same time how depressed he had been. Another participant remained sober and held a job for six months after 20 years of chronic intoxication and inability to hold a job for more than a few days at a time. There are trends, therefore to indicate that continued efforts should be made. Not only may such efforts be helpful to the chronic alcoholic offender, but also some light may be shed on other problems, such as the treatment of lower-socio-economic groups for whatever ailment.

The sociology of Skid Row was next discussed by Mr. Rooney. As a means of comparing the Skid Row society with the rest of American Society, Warner's three categories of grouping social classes was used; the professional or managerial class, the common man or permanent wage earners, and the class consisting of those regularly, but not steadily, employed. Each of these classes is linked together in society on the basis of the economic function they perform. Pressures and rewards exist to meet the standards of their group and to maintain them in that group. The non-steady workers lack two of the main ones, obtaining money to maintain an attractive way of living and the formation of strong interpersonal relations and community bonds. Weak bonds are reflected in the manner in which a wife is regarded; she maintains the home and provides sexual satisfaction. Because these needs are met by any woman, she is easily deserted. The failures of this group populate Skid Row. This recruitment from the lowest social class is obvious, since the Skid Row group doesn't reproduce itself. Skid Row is a low pressure area; living is cheap and interpersonal demands are minimal. In this population about 20% are aged and disabled without family ties who live there because of low income. Minimal workers (including hoboes) constitute 40% of the population. They work just enough to survive and are considered as moving away from society. Those who turn against society, as thieves, bums and "mission stiffs", feel the world owes them a living; this group makes up 5% of the Skid Row population. About one-third are excessive drinkers who are considered as moving towards people because drinking is carried on in social settings. The end product of this group is the "wino" who drinks daily and comprises 5–10% of the drinking group. One of the most striking characteristics of Skid Row is the phenomenon of diminished time orientation. Whereas, even migrating or seasonal workers plan one year ahead, the Skid Rower plans from one month to a few days ahead. Winos are the extreme since they are concerned with survival for the particular day only.

As a member of the team working with the chronic alcoholic offenders, Miss Scott contrasted this with her former activity, nursing in a general hospital. Striking differences described were the greater degree of involvement with the patient and the feelings of frustration and despair which periodically arise as a result of working with the difficult and myriad problems of this type of individual. The extreme degree of dependency was vividly demonstrated by the expectations of the participants. These ranged from telephone calls in the middle of the night to retrieve them from Skid Row, to making telephone calls for them or writing letters to employment agencies to explain appointments they had missed—in addition to the usual requests for money, room, board, and clothing. She noted, in this respect, the difficulty of separating realistic requests from the unrealistic ones and in making rapid evaluations of the many requests she received especially in the middle of the night. A requirement for a worker in this area is, therefore, the ability to resist the numerous strong and often subtle unrealistic requests for help and to deal with the resulting helpless feelings when realistic requests cannot be met because of lack of funds and facilities and the shortage of workers.

Memoir of William Warder Cadbury (1877-1959)*

By S. EMLEN STOKES, M.D.

DR. WILLIAM WARDER CADBURY, physician and naturalist, was one of the early pioneers in medical missionary work in China.

He was born on October 15, 1877, being the fourth child of Joel and Anna Cadbury, both of Philadelphia, Pennsylvania. He graduated from the William Penn Charter School in 1894 and later attended Haverford College from which he received his B.A. degree in 1898, M.A. degree in 1899, and in 1936 was granted the Honorary Degree of Doctor of Science by Haverford.

In 1902 he received the degree of Doctor of Medicine from the University of Pennsylvania and was licensed to practice medicine in the State of Pennsylvania that same year. Following his medical education he served as resident physician at the Pennsylvania Hospital from 1903 to 1905.

It was not uncommon during this period in our medical history to find young medical graduates seeking further education abroad, consequently he spent several months in Europe attending graduate education at the General Hospital in Vienna, Austria.

Following his return to Philadelphia, he was appointed by the University of Pennsylvania Medical School as Instructor in Pathology and Pharmacology from 1906 to 1907 and also served as pathologist to St. Mary's Hospital from 1906 to 1909.

In 1909, when the University of Pennsylvania Y.M.C.A. made plans to send a group of physicians and nurses to do medical work in China, Dr. Cadbury volunteered to join the unit, because in China with its millions of people, there were very few trained in Western medicine. The university unit aimed to establish a medical school not only to help the needy but also to develop a training school for young Chinese.

Arriving in Canton in 1909, Dr. Cadbury became associated with the Canton Christian College, later known as Lignan University, and it was here that he spent the most fruitful years of his life covering a span of 40 years.

In America many friends became interested in his work, contributing to the Cadbury Fund and also building for his use on the Chinese campus a home called the William Penn Lodge, where he and his wife, Catherine Jones Cadbury, whom he married in 1917, could receive their many guests and friends and hold discussion groups. One of his ambitions was to make the grounds and gardens surrounding this home as beautiful as possible, so he collected a representation of every type of tree and flower native to this region as well as introducing plants from other countries. After returning to this country he presented his collection of ferns to the Academy of Natural Sciences.

Soon after his arrival in Canton he and his colleagues persuaded the University's President Chung to approach the Chinese Government for assistance in establishing a medical school. With the help of the Government, the Rockefeller Foundation, and other Chinese medical schools, the Sun Yat Sen Memorial Medical School was established.

During his early years in Canton he was appointed college physician to Canton Christian College, serving in this capacity from 1914 to 1932.

With the establishment of the Sun Yat Sen Medical School of Lignan University he was appointed Professor of Internal Medicine and

* Read before the College of Physicians of Philadelphia, 2 November 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

head of this department, which position he held until his retirement in 1949.

The Japanese war interfered with the operation of the Medical School, but the hospital continued to function under Chinese management. During this period Dr. Cadbury worked with the American Red Cross, bringing relief for the bombed city. After the Japanese occupation, Lignan University had a refugee camp of over 7000 persons. After World War II started, Dr. and Mrs. Cadbury were interned and then repatriated to the United States, but when hostilities ceased he returned to Canton to help re-open the Medical School and Hospital.

In reviewing the life of our fellow member of this College, we must not neglect the many other facets of his life which endeared him to so many here and abroad. His home, the "William Penn Lodge" on the campus of Lignan University, was the center of friendship and cultural discussions. Here his three daughters Jane, Emma and Catharine were born and it was here that he wrote many of his medical articles, 130 in all, and over 230 articles on religion and other general subjects.

Among his medical articles were, "The 1918 Pandemic of Influenza in Canton", and "The Food Value of the Milk of the Water Buffalo".

He was not only a Fellow of the College of Physicians of Philadelphia (elected 1908), but also a Fellow of the American College of Physicians, and the Chinese Medical Association, serving as its Vice President from 1935 to 1937.

After his return to the United States, he resumed active interest in the work of the Religious Society of Friends (Quakers) of which he had been a member from birth.

Those who have seen Dr. William W. Cadbury at work in Canton, China, can testify to the extraordinary influence he had upon those with whom he came in contact, whether they were Europeans or Americans, like himself, or the Chinese to whom he ministered. Patients, students, nurses and doctors were his associates for forty years and they found in Dr. Cadbury a friend who was ready to listen to troubles of all kinds and a physician who brought healing and knowledge about healing wherever possible. He taught the skills he had learned himself and when the time came for him to take a subordinate place it gave him joy to see his Chinese colleagues in the places of leadership for which he had prepared them.

While it was heartwarming to see Dr. Cadbury's satisfaction in the type of life he had chosen, it was even more satisfying to see the love and affection which the Chinese people felt for him. They could see that his Christianity was genuine and that it was the force which motivated him. This was evident to all as he moved about in the hospital, or on the streets of Canton and on the campus of Lingnan University.

One of the great joys of his life was the completion of the new building for the Canton Hospital in 1935, one hundred years after medical work began in China through the valiant efforts of the medical missionary Dr. Peter Parker, and twenty-six years after Dr. Cadbury's own arrival in China.

Dr. Cadbury died on October 15, 1959. At the memorial service for him, the pastor of the Chinese Christian Church in Philadelphia said that when Dr. Cadbury passed by, people would say, "Here comes Christian good will". He preached by personal example as well as by precept, and he inspired in people Christian love, faith, hope and cheerfulness.

Memoir of Israel Pemberton Pleasants Hollingsworth (1880-1960)*

By HENRY PLEASANTS, JR., M.D.

ON APRIL 3rd, 1960, Israel Pemberton Pleasants Hollingsworth died at his home, 411 North Walnut St., West Chester, Pa., just one day before his eightieth birthday.

He was the son of the late Samuel Shorey Hollingsworth, a distinguished member of the Philadelphia Bar, and Nancy Pleasants Hollingsworth. The former was the son of Jehu Hollingsworth, inventor of one of the earliest of the repeating rifles, and Frances Shorey Hollingsworth.

Doctor Hollingsworth was a graduate of Germantown Academy and of the University of Pennsylvania School of Medicine, Class of 1903. It was particularly appropriate that he should have served his internship at the Pennsylvania Hospital, of which his ancestors, Israel Pemberton, Israel Pemberton, Jr., and Samuel Rhoads had been founders, and Samuel Pleasants a member of the Board of Managers (1779–81). Following this, he served as Resident Physician of Bryn Mawr Hospital before accepting a position on the staff of a large urological clinic in Seattle, Washington. A year or two later, he returned east, becoming the attending physician of Glen Mills School in addition to practicing physician in the neighborhood.

In 1917, he entered the U. S. Army as a First Lieutenant, Medical Corps, and served overseas in France, being honorably discharged as Major in 1919. From 1919 to 1921 he practiced in Sioux Falls, S. D., but returned after a few months to become Staff Pathologist at the Memorial Hospital, Roxborough, Pa. and a member of the teaching staff of the Graduate School of Medicine, University of Pennsylvania. Not long after this, he moved to West Chester, Pa., to assume his duties as Pathologist of the Chester County Hospital where he built this service from very little to a well-organized and invaluable department.

Dr. Hollingsworth contributed important essays covering personal observations in the fields of medicine, surgery and pathology. A noteworthy study was: Chronic Arthritis, An Appraisal, (Medical World **53:** 773–776, December 1935). Of interest to historians was his Review of the Autopsy Reports on the Body of Admiral John Paul Jones, (Medical World **53:** 305–306, May 1935).

He was a Fellow of the College of Physicians of Philadelphia (elected 1932); a member of the American Medical Association, the American Association of Clinical Pathologists, and a past president of the Chester County Medical Society. He was also a member of Delta Psi Fraternity.

Surviving Dr. Hollingsworth are his wife, the former Delphine L. Robertson, whom he married in June 1909; a daughter, Mrs. J. Charles Taney, 2nd.; two sons, Roger P. and Samuel S.; a sister, Mrs. Julian Marks, of Petersfield, England; a brother, John Pleasants Hollingworth, of Radnor, Pa.; seventeen grandchildren and two great-grandchildren. One daughter, who died some years ago, was the wife of the late Louis B. Laplace, M.D., of Philadelphia.

Those of us who had the honor of being associated with Pemberton Hollingsworth since boyhood were invariably impressed by his sincerity and honesty in all of his relations with patients and colleagues, assistants and friends. Although his professional duties were largely limited to clinical laboratory procedures and research, his ability as a diagnostician was widely recognized. The medical profession has sustained a great loss by reason of his passing.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of George Morrison Coates (1874-1960)*

By HARRY P. SCHENCK, M.D.

GEORGE MORRISON COATES died suddenly of coronary thrombosis at his home in West Whiteland, Chester County, Pennsylvania, on February 7, 1960. Keenly alert and with undimmed interest in his many avocations, he had continued in private practice at his office in Philadelphia and was engaged in his numerous editorial activities until death occurred within a month of his eighty-sixth birthday.

He occupied a preeminent and unique position in otolaryngology for more than sixty years. The weight of his support sufficed to ensure the success of many controversial innovations in the practice and teaching of his specialty. Because of his modesty, kindliness and strict honesty, he was known as "the man without an enemy", and yet, once convinced of the merit of an individual or a cause, he was an inflexible and courageous defender.

Dr. Coates was born in Philadelphia on March 24, 1874. His Quaker ancestors had settled in the Delaware Valley prior to the arrival of William Penn. Two of his ancestors were among the founders and early members of the Board of Managers of the Pennsylvania Hospital, the first hospital to be founded in the United States, and members of his family have been associated with it continuously ever since.

He spent his early years in Berwyn, Chester County, Pennsylvania, and graduated from the Haverford School, receiving the coveted prize in Greek. From the University of Pennsylvania, he received the degree of Bachelor of Arts in 1894, and the degree of Doctor of Medicine in 1897. During his college years he was active in sports, acting as captain and manager of the track team and captain and manager of the football team. As a champion bicycle racer, he received numerous cups and trophies. He was on the editorial board and served as sports reporter of the weekly college paper, and, later, was on the editorial board of the Alumni Register, President of the Alumni Society and permanent president of his class.

Dr. Coates served an internship at St. Christopher's Hospital for Children from 1897 to 1898, and at the Pennsylvania Hospital from 1899 to 1901. He began the study of laryngology with Dr. Francis R. Packard at the Pennsylvania Hospital and with Dr. Walter Roberts at the Philadelphia Polyclinic and College for Graduates in Medicine between 1901 and 1905. At the latter institution, he became Associate Professor of Otology, and with its merger with the Graduate School of Medicine of the University of Pennsylvania in 1919, he was appointed Professor and Chief of Service of Otolaryngology in the Graduate School. He was also Professor of Otolaryngology and Chief of Service in the School of Medicine and Hospital of the University of Pennsylvania from 1933 to 1939, when he became Emeritus Professor. For many years he was Chief of Service at the Presbyterian, Abington Memorial, Germantown and Chester County Hospitals.

Dr. Coates was certified by the American Board of Otolaryngology in 1925, becoming a Director in 1930, and later, senior consultant. As president of the American Laryngological Association, the American Otological Society, the American Laryngological, Rhinological and Otological Society and the American Academy of Ophthalmology and Otolaryngology he exhibited outstanding leadership and directed major permanent changes of policy.

* Read before the College of Physicians of Philadelphia, 2 November 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

In addition to fellowship in the American College of Surgeons, the American Society of Immunologists, the Pacific Coast Oto-Ophthalmological Society and the American Bronchoesophagological Association, he was corresponding fellow of the Société de Laryngologie des Hôpitaux de Paris.

He served as chairman of the section of Laryngology, Otology and Rhinology of the American Medical Association in 1927; chairman of the ear, nose and throat section of the Pennsylvania Medical Society in 1921; president of the Philadelphia Laryngological Society in 1922; chairman of the ear, nose and throat section of the Clinical Congress of Surgeons of North America from 1921 to 1936, and chairman of the ear, nose and throat section of the College of Physicians of Philadelphia from 1928 to 1930.

Dr. Coates was editor-in-chief of the A.M.A. Archives of Otolaryngology from 1937 to the time of his death; co-editor with Dr. Chevalier Jackson of "The Nose, Throat and Ear and Their Diseases" (1929); co-editor with Dr. I. S. Ravdin of the American Edition of "Kirschner's Operative Surgery" (1937), and editor of the five volume, international reference work "Otolaryngology" (1955). He was the recipient of the Newcomb Award of the American Laryngological Association in 1943 and of the deRoaldes Gold Medal in 1949; the Award of Merit of the American Academy of Ophthalmology and Otolaryngology in 1946, and the Gold Medal Award of the American Otological Society in 1949.

As Assistant Surgeon in the United States Navy during the Spanish American War, Dr. Coates served aboard the U.S.S. *New Orleans*, a second-rate ship of ten guns purchased by the Navy for the emergency. After bombarding installations in Cuba, and San Juan, Puerto Rico, the *New Orleans* participated in the Battle of Santiago Bay. He later served as Lieutenant to Lieutenant Colonel in the Medical Corps of the Pennsylvania National Guard, from 1900 to 1916, and as Major to Colonel, MC, U.S. Army, from 1917 to 1919. During World War I, he was chief of the section of head surgery at base hospitals in Camp Sevier, South Carolina, and Camp Hancock, Georgia; commanding officer of Base Hospital #56, Allerey, France; otolaryngologist to the Embarkation Camp, Bordeaux, France, and president of the Reclassification Board.

Dr. and Mrs. Coates were active in the Episcopal Church. Their home in Philadelphia was a mecca for visiting colleagues from the Americas and Europe and students were always welcomed. Perhaps his greatest interest was the teaching and counselling of young men in the profession. His advice was invaluable because of his exhaustive knowledge of the available teaching programs and of the ability of teaching personnel. Many of the advances in graduate medical education were the result of his unflagging efforts to improve methods of instruction. In addition to his wide interests in military, zoological, geographic, athletic and literary societies, he served as a member of the Executive Committee of the Boy Scouts of America, a member of the Board of Trustees of Haverford School, a trustee of St. Michael's Home for Crippled Colored Children, and a trustee of the Pennsylvania Institute for the Instruction of the Blind.

In spite of his innumerable interests and heavy administrative duties, he never seemed hurried or harassed and there was always time for a quiet chat with an unexpected visitor. He indeed possessed those attributes so admired by William Osler—imperturbability, equanimity, firmness, courage, infinite patience and an ever-tender charity toward his fellow creatures.

In his later years, the death of Mrs. Coates and the tragic death of his son were overwhelming losses but as always he met adversity without bitterness. He is survived by his daughter, Elizabeth, and two grandchildren.

TRANSACTIONS & STUDIES
of the
College of Physicians of Philadelphia

Volume 28
(Fourth Series)

Number 4
(April 1961)

Annual Report of the President, College of Physicians of Philadelphia*

By JONATHAN E. RHOADS, M.D.

THE year just closed has been a year of continuing growth for the College. Its book collection has grown; its journal collection has grown. The Medical Documentation Service had its largest year. On an overall basis the College increased its resources substantially, though not as fast as we had hoped.

Being the first year of a new decade, we addressed ourselves to the apparent needs of this 10-year period and estimated that the College should have at least another million dollars in endowment. This would mean that we would need to raise $100,000 a year during this period. Efforts were launched in three directions:

1) A general appeal to the Fellows to appeal to their patients and friends, as well as to do what they felt able to do personally was launched. A committee for this effort was headed by Dr. Thomas M. Durant, and its efforts have resulted in a substantial number of contributions.

2) A second effort developed from a suggestion by Dr. George I. Blumstein that endowments be sought for individual journals and that these journals be identified with the donors. This resulted in the establishment by Council of the S. Weir Mitchell Associats, to which Fellows and friends of the College may gain admission by a contribution of $1,000, payable over a period of one to four years for the endowment of a journal. Dr. Blumstein is the chairman of a very active committee to enlarge this group. Thirty-three Fellows availed themselves of this opportunity during the first year and it is hoped that many more will do so in 1961.

3) A third committee under the chairmanship of Dr. Lewis C. Scheffey has addressed itself to the task of encouraging Fellows and friends of the College to remember it in their wills. If every Fellow of the College saw fit to leave the College even a small percentage of his net estate, it would probably do more than anything else to build up our endowment funds to realistic levels. I believe it would be difficult to think of a better way in which to perpetuate one's desire to help the medical profession and the healing arts in general than to make such a contribution for the continuation of the College and the improvement of its Library.

The Report of the Treasurer will be published in the *Transactions & Studies of the College of Physicians of Philadelphia* in due course. Some comparative figures are shown in Tables I and II. These figures are subject to

* Read before the College, 4 January 1961.

audit. We again closed the year with a deficit in our operating account in the amount of $3,487.41 and this was whittled down to $650.84 by the application of certain gifts which could be designated for current expenses. To offset this the account for funds restricted to the Library showed a small surplus due to the Herculean efforts of our Librarian, Mr. Elliott H. Morse to increase the contributions to the Library and due to his careful husbandry of the Library's resources.

In the capital fund account it was possible to charge off approximately $3,400 of the original price of the Erlanger Garage Building through surplus from operations, from the time the building was acquired to the present. In the future Council decided to credit a sufficient portion of the earnings to the operating account to provide a 5 per cent return on the College funds invested in the garage. The other expenses will be paid and the balance used to amortize our investment.

A special anonymous gift was received for the Library through the good offices of Dr. T. Grier Miller in the amount of $10,000. This was credited to the operating account of the Library for expenditure over a three or four-year period.

Payments on account of the S. Weir Mitchell Associates amounted to $8,550 on pledges totaling $33,000. Other contributions for endowment funds, including initiation fees, totaled $6,247.50, in addition to which the sum of $5,048 was received for the Library's general endowment.

The sum of the amounts pledged by the S. Weir Mitchell Associates, the other donations received for endowment or for future expenses thus comes to $53,295.00, plus our future interest in the Zentmayer estate which may amount to $35,000.00 or more; plus $2,917.53 as special donations applied to the 1960 operating deficit in the general account of the College.

TABLE I

College of Physicians of Philadelphia Current Operating Accounts 1957–1960

	1957	1958	1959	1960
Total income	153,602	175,024	197,506	219,919
Total expenses	148,970	160,854	194,469	217,048
Income less expenses	4,632	14,170	3,037	2,871
Maintenance and reserve fund	11,104	11,501	11,897	12,311*

* Decreased by elimination of accumulated operating deficits in "general" account.

TABLE II

College of Physicians of Philadelphia Capital Funds (Book Value)

	1957	1958	1959	1960
Total	2,674,808	2,718,337	2,762,288	2,773,651*
Endowment	921,168	937,187	1,026,210	1,077,374*

* Not including S. Weir Mitchell Associate pledges of approximately $22,500.

TABLE III

College of Physicians of Philadelphia Accessioned Library Items

1950	173,450
1951	179,566
1952	181,473
1953	183,991
1954	186,852
1955	189,542
1956	192,679
1957	196,789
1958	200,349
1959	204,843
1960	208,928

TABLE IV

Library Circulation

Interlibrary Loan		Volumes Withdrawn
1,754	1950	7,172
2,342	1951	7,489
2,308	1952	7,510
2,616	1953	8,393
3,462	1954	10,218
3,532	1955	11,772
4,714	1956	11,309
6,926	1957	12,308
7,980	1958	12,993
9,161	1959	14,913
13,359	1960	17,659

TABLE V

College Library

Serials Currently Received		Photoduplications Supplied
1,477	1950	3,196
1,603	1951	2,142
1,710	1952	3,013
1,739	1953	3,438
1,930	1954	3,714
1,977	1955	4,309
2,116	1956	4,648
2,169	1957	4,432
2,169	1958	8,831
2,265	1959	5,836
2,325	1960	19,357

TABLE VI

Total Library Expenditure

(Exclusive of Med. Doc. Ser.)

1949	$38,639
1950	43,378
1951	44,640
1952	52,681
1953	56,741
1954	61,825
1955	66,187
1956	71,961
1957	75,541
1958	78,522
1959	84,525
1960	94,600

TABLE VII

Medical Documentation Service

	Income	Expenses	Subjects Scanned	Articles Reported	Translations
1958	$24,020	$23,343	25	3,996	187
1959	49,387	48,334	23	5,618	127
1960	69,896	62,078	29	9,162	140

Even in the total of $91,000.00 these amounts fall somewhat short of the $100,000.00 which we hoped to see committed to the College each year and it must be remembered that about $13,000.00 of this is expendable under the conditions of certain gifts.

Bequests were designated in the Estates of Walter G. Elmer ($500. to endowment) and William Zentmayer ($10,000. to the Library).

TABLE VIII

Staff Size

	Library	M.D.S. Full Time
1950	10	
1951	10	
1952	11	
1953	11	1
1954	12	2
1955	12	2
1956	13	1
1957	13	1
1958	14	2
1959	14	2
1960	14	3

TABLE IX

Itemized Library Expenses

	Books	Serials	Binding	Supplies	Salary
1949	$3,033	$9,972	$2,644	$1,673	$21,315
1950	3,484	10,555	3,281	1,440	24,616
1951	3,252	9,746	3,434	1,959	26,248
1952	3,958	11,229	3,423	2,190	31,879
1953	5,397	10,450	3,486	2,223	35,183
1954	3,952	14,094	3,523	3,471	36,784
1955	5,173	13,609	2,950	5,627	38,817
1956	5,218	13,216	3,632	5,919	43,975
1957	6,440	13,593	4,903	5,723	46,372
1958	6,122	14,428	4,574	7,290	47,227
1959	7,187	14,447	3,930	10,236	52,787
1960	7,170	17,826	4,694	7,075	57,712

Under the will of William Zentmayer, the College is to receive one-ninth of the residuary estate after certain life interests have been satisfied, and a preliminary estimate suggested that this might amount to over $35,000 additional.

The high rate of turnover in the personnel of the Library has been a continuing cause for concern. The scale of salaries in the Library was revised upward two years ago, but it became evident during the current year that it was still unrealistic. Our Librarian made a survey of practices in similar institutions in other cities. He obtained statistical material from the Medical Library Association, and he made inquiries concerning starting salaries for individuals completing professional training in

TABLE X

ITEMIZED LIBRARY INCOME

	Appropriation	Income	Receipts	Contrib. Plan
1949	$7,625	$19,214	$2,112	$3,700
1950	15,000	20,651	1,744	3,886
1951	17,823	22,320	2,331	4,897
1952	21,701	23,595	1,922	3,797
1953	25,484	22,899	2,250	5,618
1954	26,858	23,271	2,648	5,289
1955	28,026	24,457	8,649	4,845
1956	32,698	25,730	6,465	6,297
1957	32,391	27,999	11,075	7,932
1958	31,921	32,351	8,178	13,402
1959	32,412	32,329	14,090	11,622
1960	32,330	33,956	9,575	16,317

TABLE XI

COLLEGE OF PHYSICIANS OF PHILADELPHIA MEMBERSHIP 1957–1960

	1957	1958	1959	1960
Active	988	1,037	1,031	1,045
Non-Resident	132	136	135	144
Associate	1	—	—	—
Honorary	7	8	8	7
Honorary Associate	2	2	2	2
Total	1,130	1,183	1,176	1,198
New	51	65	54	50

library science. On this basis a new salary scale was devised and approved by the finance committee and by Council for implementation January 1, 1961. The considerable amount of money required for this purpose is expected to come in part from surplus of the Medical Documentation Service which amounted to $7,818, and in part from increased contributions which have been secured both from industrial users of the Library and from the Medical Schools which it supports.

One of the most notable developments of the past three years has been the contributions from the six schools of medicine in the city. These began three years ago but were somewhat irregular; however, now a general consensus has been reached that each school should contribute $2.00 per student enrolled. While the amount of money is not a large one, it is very meaningful for the Library, but perhaps even more important is the anticipated increase in the use of the Library by medical students. They may now receive borrowing privileges on authorization of the dean or his deputy. Most deans, I believe, are deputizing their librarians to sign these cards.

The increased usage of the Library, as the Library's Annual Report which is to appear in the April issue of the *Transactions & Studies* will show, is illustrated in the accompanying tables (III to X). Accessioned items have grown by over 4,000 to a little under 209,000 volumes. Unaccessioned items, which include reports and theses, have increased by 410. The increase in the accessioned items consists in 1,264 books and 2,686 bound periodicals. Sixty new serial titles have been added to the list of material received currently, bringing the total to 2,325 serials. The total number of books and journals consulted in the reading room has risen sharply from just under 60,000 to 84,500. The number of volumes actually withdrawn has increased from 14,913 to 17,659.

Perhaps the most startling increase in library service is revealed by the increase in the number of photoduplications supplied—from 5,836 to 19,357. This is attributed to the advent of the Xerox 914 Photocopier, which arrived in June of 1960, and which has been financed by a special grant from the Smith, Kline and French Foundation. The interlibrary loan use of the collection has risen from 7,980 in 1958, to 9,161 in 1959, to 13,359 in 1960.

The accompanying tables also indicate how expensive our library has become.

In closing this section of my report may I leave with you as a parting thought this quotation from the 1892 Presidential address delivered by S. Weir Mitchell, "you see, therefore, how large, how varied, how expensive are the wants of a great library—yet you must in reason expect your library to make even larger demands for money. It is an expensive necessity."

The Mütter Museum has been visited by a great number of people each year, and the College Collections have received as additions many interesting objects of historical interest.

Dr. T. Grier Miller had a substantial balance of over $16,000 of funds raised for another purpose—but not required for it—transferred to the account of the College by the donors more than a year ago. This made possible the purchase of completely new seating for Thomson Hall and Cadwalader Hall, and enabled our Building Superintendent, Mr. George S. Allen, and his staff to complete the seating of this Hall a year ago. Mr. Allen has also re-wired and re-hung virtually all of our collection of portraits during the past year.

The various Sections of the College have been unusually active and the Section on Public Health, Preventive and Industrial Medicine in conjunction with the Pennsylvania Chapter of the American Public Health Association presented to the College the sum of $5,000 to endow a Lectureship in honor of the late Colonel Arthur Parker Hitchens. Support of this, the College's 8th endowed lectureship, began in 1956 and was completed in 1959.

The *Transactions & Studies* of the College reflect the high caliber of the lectures delivered at our general sessions and the excellent editorial work of Dr. Fred B. Rogers. At its last meeting Council authorized the Publication Committee to accept advertising material approved by it for a limited trial period to help defray the ever increasing costs of printing.

The membership of the College is shown in Table XI. It stands at a new high of 1198 yet its growth has been conservative as the Table shows.

Thus, in every department the affairs of the College have advanced, and perhaps the most important advance of all has been the sharply increased use of our rich Library resources. The statistical data are briefly recapitulated in the accompanying tables.

The gains which the several departments of the College have made are due to the efforts of many people. I would like to pay tribute especially to the senior members of our staff, the Librarian, Mr. Elliott H. Morse; the Curator of the Library's Historical Collections, Dr. W. B. McDaniel, 2d; the Clerk of the College, Miss Olga E. Lang; the Building Superintendent, Mr. George S. Allen; and the Curator of the Mütter Museum and Custodian of College Collections, Mrs. Ella N. Wade.

I would like to thank my fellow Officers, Vice-President Thomas M. Durant, who succeeds me tonight, Secretary Thomas E. Machella, and Treasurer Jacob H. Vastine, 2nd, as well as the Censors, Councilors, Committee Chairmen and Committee Members, and the Chairmen, Clerks and Executive Committee Members of the five Sections, totaling 98 Fellows this past year, who have carried such important shares in the work of the College.

One of the great services which the College performs is to bring representatives of the five medical schools and the Graduate School of Medicine into frequent contact in working for our common goals in medicine. I have particularly appreciated this feature in the work of the College.

It was indeed a great honor to serve as your President and like the last six Presidents, all of whom are active, I hope I may continue to serve the interests of the College as long as I live. It is an institution with a great past, but we should never forget that in all probability it has an even greater future.

Inaugural Remarks*

By THOMAS M. DURANT, M.D.

Dr. Rhoads, Fellows of the College:

IN ACCEPTING the gavel representative of the Presidency of this College I am fully aware of the honor you have bestowed upon me. At the same time I am cognizant of the responsibility that is now mine in assuming leadership of this highly respected organization. Throughout the years since the founding of the College in 1787 it has played an important part in the dissemination of medical ideas and knowledge, and in the production of ever higher standards of medical practice. Each of our many distinguished presidents has given unstintingly of his talents and energies and has established records of achievement that make me feel very humble. Our retiring president, Dr. Rhoads, has recognized the need for a greatly increased endowment of our splendid library, and you have heard from him about the wise three-point program he has instituted toward this end. Already tangible results are evident, but, if it is to fulfill Dr. Rhoads' hopes, this program will require continuing vigorous effort on the part of the several committees involved, and full cooperation on the part of the Fellows. I am convinced that the rewards of such a prosecution of the program will be great and will enlarge the College's contribution to Medicine. For this reason it is my avowed intention to carry on the work so well begun by Dr. Rhoads.

I am more than pleased that I may count on the whole-hearted support of the excellent Vice-President you have elected, Dr. John H. Gibbon, Jr. I am also pleased that our Secretary, Dr. Machella, and our Treasurer, Dr. Vastine, will be continuing in office the fine work they have been doing for the College. Their experience will be invaluable to me.

In conclusion, I feel I must express some degree of apprehension that its Fellows, in recent years, have tended to take the College too much for granted, forgetting that the privileges of membership in an organization like this one are available to only a small proportion of the physicians in this country or in any other. It is my sincere hope that this tendency will be reversed and that there will be a considerable increase in your participation in all College activities. I can guarantee that the result will be a most worthwhile one, not only from the standpoint of the College, but from yours as well.

* Remarks of the incoming President, 4 January 1961.

FIG. 1. Dr. Jonathan E. Rhoads, retiring president, presents the gavel of office to the incoming president, Dr. Thomas M. Durant.

Two Landmarks in American Medicine—Their Impact[1]

By TRUMAN G. SCHNABEL, M.D.[2]

TWO very important influences have been brought to bear on American medicine since the turn of the century. At that time, and for a decade or more, thereafter much concern was had for the status and fate of medicine in this country. It was maintained that too many doctors were being turned out by too many medical schools and that the performance of the American doctor was growing less and less impressive because of his relatively brief exposure to inadequate and outdated curricula.

In 1905 there were 160 medical schools functioning in the United States with an enrollment of 26,147 students, of whom 5,604 were graduated in that year. Of these schools, twelve were located in Missouri, fourteen in Illinois and, surprising as it may seem, eight were carrying on in our own state of Pennsylvania. Only thirty of these 160 schools offered reasonably good training opportunities in medicine. They devoted a good portion of their schedule to didactic teaching, but also arranged for some work in laboratories and were using some clinical material in all hospital departments for teaching purposes. In some of this better group of medical schools, extra mural quizzes flourished and unhappily still, seemed to be a necessary adjunct to the intramural program.

Most of the remaining schools were highly commercial and had enjoyed a profitable business until the first years of this century when their yearly incomes were averaging less than $10,000. Their teaching rosters were given over almost entirely to didactic teaching during school sessions that were overly short. Admission to many of the poorer group of schools did not even require a high school diploma. No thought was given to the articulation of the medical school with a university or with the educational system generally. Nothing in the existing scheme of things suggested the importance of the basic sciences to a medical student, or later on, to the practicing physician. Medical education was not regarded as a serious and costly venture and it was observed not too infrequently that a young man having failed in other fields, turned to medical school as a last resort.

One of my room mates in medical school had graduated from Bucknell University in 1906. He took on a position in a bank immediately after receiving his diploma from that institution, but less than six months had passed by when he decided that banking was not to his liking and so determined on medicine for his career. Hoping to save some time, he enrolled in a school whose first term began after New Year's day. In due time, he appreciated that he had chosen a diploma mill for his medical school and then arranged to begin anew here in Philadelphia in the fall of 1907. He referred on many occasions, to the shortcomings of his former school as lamentable. I remember on one evening, after spending a profitable day dissecting the brachial plexus for himself in our anatomical laboratory, that he recalled a day in the previous year when the whole class crowded around a lone instructor as he demonstrated the brachial plexus on a dried specimen on which one could hardly distinguish one structure from another, even though standing immediately at the demonstrator's side. This room mate of mine ranked sixth in our class on graduation and subsequently practiced medicine with distinction, in Western Pennsylvania.

[1] Read before the Section on Medical History, College of Physicians of Philadelphia, 15 November 1960.

[2] Emeritus Professor of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

Fortunately for American medicine and so for the people of our country, Abraham Flexner made a careful study of medical education in the United States and in Canada while my room mates and I were struggling along with our studies in Medical School. This brilliant investigation was sponsored by the Carnegie Foundation for the Advancement of Teaching, and its findings and instructions were presented to the Foundation in 1910. The strictures in this celebrated report were so biting that many of the weaker schools were obliged to merge with other schools and the commercial medical schools with their alluring advertising campaigns were compelled to go out of business. Very few believed any longer that the existence of a poor medical school was justified for the sake of needy medical students.

By the time 1922 rolled around there were only eighty-one schools left with an enrollment of 15,635 and a nation-wide graduation class of 2,529. Clearly then, fewer doctors were being turned out by half the number of schools that had been operating seventeen years previously. There were only seventy-six schools left in 1931. Forty-nine years after 1905 the number of graduates in medicine again exceeded 5,000 a year for the first time, while the population of the country had increased by more than 65,000,000. During the school year of 1959 and 1960, 29,793 men and women were enrolled in eighty-one four year medical schools and 7,081 of these students received their degrees in June last.

The Flexner report pointed out that an overproduction of doctors by a poor lot of medical schools accounted for an overcrowding of physicians the country over, even though there were then, as there are now, communities without the attendance of a single doctor. It pointed out at the same time, that the superfluous doctor ordinarily is a poor one. In keeping with this contention, it was emphasized that in all likelihood, the one doctor to 2,000 people in a large city would be four times better than the one doctor who might be caring for 500 people. What makes for a good doctor was not clearly indicated. While the report did not suggest any doctor of medicine to population ratio which might represent good medical coverage in this country, one gains the impression that Flexner thought the existing ratios in Germany should be right in the United States as well. Perhaps the ratio in our largest cities might then range from one to 1,000 on up to 1,500, and elsewhere, one to 2,000 people.

It may or may not be surprising that I, being the son of a general practitioner in upstate Pennsylvania, and studying medicine in Philadelphia, was never made to feel that there were too many physicians carrying on during the first decade in this century. My native town was one of five adjacent boroughs whose total population was 20,500 in 1906 where forty-three physicians were available for its medical needs and those living on the surrounding farm land. The population of these boroughs now merged into a city, was 66,340 in 1958 and 132 doctors were on hand, according to the American Medical Association directory of that year. This means that the ratio of all doctors of medicine to this community's people was one to 453 in 1906 and one to 502 in 1958. The same sort of ratios were one to 450 for Philadelphia in 1906 and one to 429 in 1958, one to 666 for Pennsylvania in 1906 and one to 565 in 1958, and one to 700 in 1906, and one to 749 people in 1958 for the country at large.

In this connection, it may be that potential medical care is more easily comprehended when expressed in terms of physicians per 100,000 people. If so, then one doctor to a population of 500 is the equivalent of 200 doctors for 100,000 people, one doctor to a population of 1,000 is equivalent to 100 doctors for 100,000 people and one doctor to a population of 2,500 means that forty physicians stand by for 100,000 people.

There is, as you must know, much concern again about the number of doctors in this country, but this time it is for their shortage in number. The ratios I have mentioned, however, do not seem to substantiate such a

situation because there is very little difference, if any at all, between those that apply now and those of fifty years ago. Remember that too many doctors were thought to be on hand fifty years ago.

I must confess that I did not have any idea again that the number of physicians here and elsewhere in the United States is at fault. True enough, the laity complain of the scarcity of physicians when they are unable to contact a doctor in an emergency, and sometimes they point to the crowded reception rooms of doctors as evidence of a dearth in their numbers. Usually, such doctors see their office patients, first come, first served. Of course, one can not accept such testimony as evidence of a doctor shortage.

I think at times, that I did not feel the doctor shortage because I lived and still live and practice in the fourth largest city in the country. Of the different political subdivisions, the largest cities always have the greatest number of physicians proportionate to their population. This number shows a tendency to grow less and less as one moves, in consideration, to smaller cities, to suburban and rural areas, into the states themselves, and finally, the smallest number of doctors per 100,000 population holds for the country at large.

Be all of this as it may, I only sensed a lack of M.D.'s in this country, after I read of a recent report made by a competent consulting group to the Surgeon General of our country. In its report, two problems were emphasized. First of all, a critical shortage of doctors which is becoming more serious each year and second, a steady deterioration in the quantity, as well as the quality of students who are applying for admission to medical schools. The number of such applicants has decreased alarmingly because there were 9,266 fewer men and women who tried for medical school admission last year than ten years ago. Besides this, their academic qualifications have been considerably poorer as measured by the number of grade "A" students who have been applying for admission and by their scores as measured by the Medical College Admission Test.

Abraham Flexner, who died in September 1959, at the age of 93, lived long enough, I am sure, to learn that the great improvement in medical education and the decrease in the number of medical schools which followed his report never did change the doctor of medicine or M.D. ratios to population in too significant a way. This was fortunate, I should say, because if over the years the production of physicians had been much less than it has actually been, then we would now be in a most unfortunate position indeed. Flexner, however, did not expect, I am sure, that the medical profession would take on other responsibilities than those of caring personally for the physical and mental welfare of our people, or perhaps better said, of the family. It now develops that 25,000 doctors of medicine are spending their full time or a part of it, in teaching and research, 16,000 are serving in the military, 2,300 in state and local health departments, and the same number, or even more, are engaged in industrial medicine and the administration of hospitals and other organizations and institutions. This sizable group of physicians obviously does not practice medicine in the conventional manner and so should not be included in calculations for the determinations of practicing doctor-population ratios. If then, one only considers practitioners of civilian medicine for such purposes, the Pennsylvania state M.D. ratio becomes one to 1,045 instead of one to 565, and the similar national ratio becomes one to 1,081 instead of one to 749.

These differences in ratios do clearly spell out what must be an appreciable increase in the present practice load for those who carry it. Furthermore, if one believes, as one must, that general practitioners are the backbone of practice today, then reckoning with their number will yield the really important current ratios. By doing so, it develops that a ratio of one to 1,048 becomes one general practitioner to 2,636 people for the state of Pennsylvania. As far as the whole country is concerned, the ratio of one practitioner to 1,081 becomes one general practitioner to 2,548 people. Such

striking ratios are red lights for those who organize medical education and are responsible for the health of the people of the United States, or any of its subdivisions.

These figures naturally raise the question as to how many general practitioners are needed to afford the best sort of medical care for a given number of people. This is a difficult question to answer because it is well known that the medical needs of a community always vary from time to time and will depend on its location and census, whether fixed or changing.

Fifty to sixty years ago most of the medical profession was doing more or less the same thing, namely, general practice. There were a few men who limited their efforts to a special field, research was only occasionally avocational and teaching almost entirely part time. The standing army was small, and all the other new fields of interest for the doctor were just opening.

I submit that the family physician would not be able to carry the load of general practice today, were it not for a number of circumstances, among which is the jurisdictional encroachment of the facetiously styled "general specialist" on the field of the general practitioner. Besides this, fewer doctors are now required for the care of a given number of people than was true earlier in the century before the automobile and telephone made their job easier and less time consuming. Fewer doctors are also needed now to cover house to house and office practice because a great deal of such work is being shifted to the in and out-patient departments of hospitals, whether the sick are in possession of insurance contracts or not. Patients are cared for more conveniently and satisfactorily in hospitals in a large measure because of their sizable resident staffs, not to mention their visiting and nursing staffs, laboratory and X-ray facilities. Little wonder, all of this, if one considers alone the fact that there were 37,784 interns and residents, native and foreign, training and helping in the work of the approved hospitals of the United States in 1959 and 1960.

Easement in practice has also come about because of the availability of the wonder drugs. Finally, some of the slack in practice is being taken over by those in a varied lot of paramedical professions. Here we have the Public Health Visiting Nurse, the Medical Social Worker, Occupational and Physical Therapists, Clinical Psychologists, Nutritionists, Vocational Rehabilitators, Chiropractors and Naturopaths, not to forget the potential of 14,000 licensed Osteopaths.

My father, a general practitioner, in the days before and after his telephone and air-cooled Franklin, delivered in his heyday an unbelievable number of mothers each year in their homes. Today 90% of deliveries are conducted in hospitals. Besides his obstetrical practice, he cared for patients with all manner of diseases, including pneumococcus pneumonia, tuberculosis in various parts of the body, meningococcus meningitis, typhoid, scarlet fever, diphtheria, rheumatic fever and functional disturbances as they occurred in the young and old. I remember also that he cared for small pox victims on several occasions, that he always treated fractures and dislocations, practiced minor surgery and exodontia. All of these services, of course, required time, were frequently carried out at a distance from his home and office, in fair weather and foul, night and day.

As for myself, when I served my internship, or what was then styled a residency in a hospital of 350 beds, there were twelve residents to carry on and two other residencies of two months each were open in gynecology and obstetrics. This made for a ratio of one house staff doctor to twenty-five patients. At present, with a bed capacity of 810 and sixty-eight bassinets, this same hospital has thirty-two medical interns, two dental interns, 212 residents and thirty fellows. So, now there is one house staff doctor to two patients. The hospital had approximately fifty-six unfilled residencies last year.

Thus far, then, it is evident that the Flexner

report was responsible for a reduction in the number of graduates in medicine for a number of years. In due time, however, their number gradually increased again, so that together with the prolongation of the doctors' life expectancy, the number of M.D.'s was made to keep pace for a while with the steady increase in population. But now, even though there were 226,635 good doctors with us in 1958, over against 121,434 in the crowded medical scene of 1906, the number of physicians is nevertheless insufficient to meet the present day all around need for the doctor of medicine.

Whatever else may be said about the influence of the Flexner report on the medical situation in this country, there is no doubt of the almost revolutionary influence it had on medical education. Here, significant changes were effected almost immediately after the report's appearance, so that the medical student was promptly exposed to the best pedagogic technics of the day, as well as the rapid advances that were being made in medicine. The basic sciences began to play a larger role in medical training programs and more student hours were spent in the laboratory, at the bedside, in clinics, and fewer on hard benches. Schedules over the years began to allow more time for faculty guidance, self-orientation and, of course, student investigation and research.

It was during my undergraduate days that the first Undergraduate Medical Association in the country was organized in my school. Our gynecologic professor, John G. Clark, having the idea, sponsored the organization. Its first session was devoted to organization and to a surprising program consisting of students' reports on their investigative achievements.

The Council on Medical Education followed by the Council on Medical Education and Hospitals, as might be expected, promptly established minimum standards for training, both in medical schools and hospitals. At almost the same time, the Council began to have surveys made of medical schools with a view of keeping them up to required medical standards. To begin with, medical schools were graded alphabetically and their grades were published. Now, however, they are apprised of their omissions and commissions, the needed corrections made, and happily no publicity is given to the matter. Whether because of such practices or not, I believe that it can be said that our medical school curricula in this country have in a large part, become increasingly better and better, and now can be rated with the best in the world, all of which was originally triggered by Abraham Flexner and his studies.

I entered Medical School in 1907, about the time the picture was changing. As a matter of fact, my class was the last one whose members were admitted on the strength of a high school diploma alone. Admission to classes after mine called for one, two, three and finally, four years of college work with evidence of having studied a stipulated amount of chemistry, physics and biology. Under these circumstances, there was a rush for admission to my school in 1907 when 187 men were admitted to the first year class. During the following four years, sixty members of this original group either left school or failed scholastically. Twenty-four replacements, however, were accepted by transfer from other medical schools, so that 151 diplomas were finally bestowed upon my class of 1911. It had experienced an attrition rate of thirty percent in four years which would embarrass any medical school dean of this day no end. The class of 1915 graduated fifty-nine young doctors.

During my first year as an undergraduate in medicine, there were 605 men on the student roll of my school and the names of 160 teachers were listed as officers of instruction. In 1959, the school roll showed the names of 509 men and women just ninety-six fewer than there were fifty-two years previously. At the same time, 1,226 names were listed as officers of instruction with various teaching ranks, among which were 340 with some sort of a professorial rank. Besides these

officers of instruction, the school bulletin listed the names of twenty-three active preceptors scattered across the country and some residents who, it appears, did some teaching, but were not given an official teaching rank. In other words, during my first year in medicine, there was one teacher available for 3.7 students, while now there are 2.5 teachers on hand for one student. Such a large sized teaching staff certainly must have a decided edge on the one of my undergraduate days, over fifty years ago.

While the undergraduate situation was being well organized and oriented, the same could not be said of graduate or even continuation training for the doctor at some time or other after his intern days. Opportunities were offered for such training but there were comparatively few takers until the specialty boards were organized and began to function. The boards, for the purposes of this presentation, constitute the second landmark in American Medicine.

Even before the boards began to examine candidates, it was felt that medical graduates and then interns, should have had more training than five or six years permitted before he or she had to face private practice. Nothing was done, however, to meet this need because there was even then, much complaint about the late time in life before the young doctor could begin his life's work.

However, with the demands for additional training, as required of candidates for board examinations, came the development of resident training programs in hospitals everywhere. Such training programs quickly took over the role of private preceptors for those who desired special training. Besides resident training programs, graduate schools began to offer some formal programs while medical societies and hospitals in time arranged a great number of shorter and less formal courses, seminars, et cetera. Added to such opportunities, were the medical society programs that gradually took on a post graduate air.

Little or no use was made, early in this century, of the word, specialist, as applied to a physician who was particularly knowing and skilled in a limited field of practice. Again, going back to my native town, I remember that there were only two physicians who limited their practice to a special field, or better said, to special fields, namely that of the eye, ear, nose and throat. The local hospital was more or less of a totalitarian institution at that time, in which one physician in charge almost single handed, cared for all patients irrespective of their diseases although his greatest and finest skill was surgical. Forty-three general practitioners referred their patients to the hospital, but never even had private room privileges. In some nearby cities, however, some of the hospitals were departmentally staffed by men who achieved to a reputation as consultants.

I have no idea how many men there were here in Philadelphia in the early years of the century who really limited themselves to certain fields of practice, or who were, to quote the laity, "used as consultants". I think it can be assumed that departmental heads in the Medical Schools limited their practice with a fair degree of strictness and that non-teaching hospital chiefs did likewise. There were other physicians who in the course of a general practice, developed on their own, a reputation in some special field, which was justified by exceptional knowledge or skill in that direction. This is still thought by many to be the best approach to specialism, namely, by way of the general practice route. Sometimes the move to special practice was a self-declared one after having taken a short course away from home or here in Philadelphia. There were some out of towners who spent a month or two here in Philadelphia and then went back home as full fledged consultants, according to their local news sheets. Whether or not the laity appreciated how able the consultants were in those days, is difficult to say, but many of the profession itself could not believe that a short course of a month or two either in Vienna or in our old

Polyclinic Hospital on Lombard Street, was enough to make a thorough going specialist in any field.

So it was that in 1913, leading ophthalmologists in this country felt strongly that no short time spent abroad or anywhere in this country would enable one to acquire the special skill and knowledge which an ophthalmologist should have. These men, accordingly began to establish standards in their field and organized the first specialty board in this country in 1916. Other boards were founded in 1924 by Otolaryngologists, in 1930 by Obstetricians and Gynecologists, and in 1933 by Dermatologists and Syphillologists. These four boards set the pattern for all of the certifying boards which were to follow. The advisory board of medical specialists was organized in 1933 and 1934 and began to function actively with the result that all told, eighteen examining boards have been approved and are now carrying on effectually.

On the whole, the boards are examining groups that only profess to pass judgment on the competence of candidates who may desire to be certified in special fields of practice. The examiners recognize the limitations inherent in examinations of any type whatsoever, but feel that no one has suggested a better method of passing on the knowledge and capabilities of their candidates.

None of the boards, as far as I know, aim to determine who shall or shall not practice in any special field, and the boards are not concerned with any mechanism that would gain special privileges or special recognition for those who are board certified. Besides this, it is not the intent of boards to define requirements for hospital staff membership or advancement thereon. The boards also have had no intention nor do they have any thought of interfering with the practitioners of medicine in any of their regular or legitimate activities. The boards, for the most part, insist that the responsibility of acquiring knowledge rests with the candidate while the responsibility of maintaining standards of knowledge required for certification rests with the boards.

Under all of these circumstances, with board blessings on the hospital as a good training ground for specialization, hospitals have taken on a new look. A variable percentage of their residencies are filled, depending at times on the visiting staff's reputation as a teaching group, sometimes on physical facilities or location of the hospital and many times, on the resident stipend. On September 1st, 1959, there were 25,531 residents training in 1357 approved hospitals in this country. On the same day, there were 4143 vacant residencies in these same hospitals. Unfortunately, or otherwise, 6912 of the residents on that date were graduates of foreign medical schools and when one adds 2545 foreign interns to this number of men and women, it develops that we had here at that time, 9457 house physicians who were not citizens of the United States.

Another almost unbelievable aspect of our American medical scene today relates itself to the number of physicians who declare that all of their time is devoted to the practice of a specialty and that of this group, a large number are board certified.

Taking another look at my native city, the pertinent directories show that 132 physicians were on hand in 1958 and that of this number, forty-six were full time self-declared specialists and thirty-nine of them or 29% of the city's doctors were board certified. Nine of this specialist group were concerned with industrial medicine alone. What is fortunately gratifying about medicine in my native city now, is that its hospital is departmentally staffed by a very able group of physicians. This situation is reflected in the high caliber of the doctors in the community, whether on the hospital's courtesy staff or not. The forthcoming directory of Medical Specialists will provide listings for almost 70,000 Board Certified Diplomates the country over.

The last American Medical Association

directory credits Philadelphia with 4,833 physicians of whom 2,192 declared themselves to be full time specialists with 1,905 or 30% of the city's doctors board certified. There were 14,507 physicians in Pennsylvania in 1958, of whom 7,204 were full time specialists and 3,741 or 25% of the state's doctors were board certified. Nationwide in the same year, there were 210,027 concerned more or less with practice, of whom 77,659 were full time specialists and 57,200 certificants or about 27% of the country's doctors had been certified by one board or another.

There are those who are quite unsympathetic with the Specialty Boards' "raison d'etre" after they learn of such figures, and even before doing so. Some would say that the number of board certified physicians, mounting at the expense of the general practitioner quota, speaks badly for American Medicine in the future, knowing that there always should be a family doctor. Many are wont to comment on the eagerness with which young doctors strive for certification believing that many candidates are only motivated by the great desire to obtain a "scrap of paper", and what it may carry with it.

It must be conceded, however, that at least one fourth of the doctors in this country having had additional exposure to some sort of medical education, and practical training beyond that offered in undergraduate schools of medicine and hospital internship, must surely be much better doctors for this than they would otherwise be. I am surprisingly impressed by the confidence and know-how that the immediate post-resident shows in offering himself to his patient problems when he begins on his own. This is particularly evident in the immediate past surgical resident in doing his earlier operations of the type in which he may have had his training. In preboard days, the average doctor took at least ten years of practice to reach the reasonably full stature of a general practitioner and more years before he could take on the role of a satisfactory consultant in one field or another.

It must be conceded further that the existence of the boards has served to bring about an overall lift to American Medicine. This has been accomplished in spite of the fact that the boards are primarily examining bodies which have not for the most part, attempted to guide or direct matters for the doctor whether before his graduation from Medical School or at any time thereafter. The boards have undoubtedly served as an indirect and continual spur to all those responsible for medical education after internship and even before.

The boards merit a vote of thanks if for no other reason than that now the laity as well as the medical profession itself has in the mark of certification, evidence of more than ordinary ability to practice in a special field or other, as judged by other competent physicians in this same field. The laity can also be assured thereby that specialization has been preceded by special training in and guidance along essential lines. It finally can be said that the American doctor is equipped much better than he has ever been here-to-for because of a number of reasons, chief of these being the telling influence which the Flexner report and the American Boards have had on the whole of American Medicine, especially on medical training and education in this country.

I am indebted to the several directories of the American Medical Association and the Medical Specialties, as well as, Abraham Flexner's report published in 1910 by the Carnegie Foundation for the Advancement of Teaching. I have also drawn on the "Memorandum to Candidates for Admission to Examination", as issued by the American Board of Internal Medicine.

Memoir of Charles Howard Miner (1868-1959)*

By GEORGE MORRIS PIERSOL, M.D.

THE death of Dr. Charles Howard Miner of Wilkes-Barre, at the age of 91 years, on July 12, 1959, deprived the Wyoming Valley of a great physician, his native state of Pennsylvania of a truly public-spirited citizen, and those of us who knew him of a loyal friend. A review of Dr. Miner's career provides conclusive evidence that throughout his professional life he was dedicated to the practice of medicine, the problems of public health, and the welfare of those about him.

Dr. Miner, born in Wilkes-Barre, Pennsylvania on July 5, 1868; the son of Charles Abbott Miner and Eliza Ross Atherton, was descended from hardy pioneer stock. Many of his ancestors took a prominent part in the early history of the Wyoming Valley.

After attending the Wilkes-Barre Academy, Dr. Miner received his B.Sc. degree from Princeton in 1890. Three years later, in 1893, he received the degree of Doctor of Medicine from the University of Pennsylvania. For a year and a half thereafter, young Dr. Miner served as an intern at St. Agnes Hospital, Presbyterian, and Children's Hospitals of Philadelphia. In these hospitals he came into contact with some of the best known practitioners and pediatrists of that period. Impelled by an interest in medicine and determined to obtain the best medical education available at that time, Dr. Miner went to Europe for a year of study at the popular medical clinics of Heidelberg and Vienna. Upon his return to this country, Dr. Miner, unmoved by the lure of practice in a large city, decided to follow the laborious road of general practice in his home town of Wilkes-Barre. Here, almost until the time of his death, he continued in the practice of his profession.

The outbreak of the Spanish-American War early in the spring of 1898 interrupted his activities. Yielding to his patriotism, on May 5, 1898 he entered the Army as Assistant Surgeon to the Ninth Regiment of Pennsylvania Volunteers. His military career was brief, terminating with his honorable separation from the service on October 29, 1898. Dr. Miner returned to Wilkes-Barre and resumed his practice, the success of which justified the years of earlier educational effort. In 1904, he married the former Grace Lea Shoemaker who contributed in no small measure over the years to Dr. Miner's continued professional accomplishments.

In spite of the exacting demands of a general practice, Dr. Miner never allowed his interest in matters of public health to lag. At the turn of the century tuberculosis headed the list of the nation's urgent health problems. It was not surprising, in view of his abiding interest in tuberculosis, for Dr. Miner to become a leader in the fight to control this infection. In 1906, he was largely instrumental in founding the Wyoming Valley Society for the Prevention and Treatment of Tuberculosis. He served this organization as President from that time until his retirement from office in 1948 when he was named President Emeritus. Dr. Miner's contributions in the field of tuberculosis so aroused the interest of the late Commissioner of Health for Pennsylvania, Dr. Samuel G. Dixon, that he invited Dr. Miner to outline a system of tuberculosis clinics for the state. The first such clinic to be established was in Wilkes-Barre where the Wyoming Valley Society already organized under Dr. Miner and a group of leading citizens, became the first

* Read before the College of Physicians of Philadelphia, 7 December 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

state tuberculosis clinic in 1907. This clinic proved so successful that Dr. Dixon adopted the plan of establishing similar clinics, using Clinic Number One as a model, in every county in the state, with Dr. Miner in charge as State Medical Director of Luzerne County. He held this position until 1923. Earlier, between the autumn of 1918 and the spring of 1919, during the devastating influenza epidemic, Dr. Miner added to his many obligations by taking charge of the hospitals in Luzerne and Columbia Counties.

When, in 1923, Governor Pinchot took office, he appointed Dr. Miner State Secretary of Health. He carried out, with marked success, the duties of this assignment until 1927, especially developing the tuberculosis clinics and emphasizing special training for health officers. He was again appointed State Medical Director of Luzerne County by Governor John S. Fisher, a post which he held for two years.

At the conclusion of his duties as Secretary of Health, Dr. Miner enrolled in a course of graduate training in cardiology at the Graduate School of Medicine of the University of Pennsylvania. Although for years recognized as an authority on diseases of the chest, notably tuberculosis, it was not until after this course in cardiology and a similar course at Harvard Medical School that he specialized in diseases of the heart.

The Angeline Elizabeth Kirby Memorial Health Center was founded in 1928 by the late Fred M. Kirby in memory of his Mother. In the planning and organizing of this highly successful project, Dr. Miner played a major role. He was the first Secretary of the Board of the Kirby Health Center, becoming President of that Board in 1946, a post which he filled with distinction until his retirement twelve years later when he was made President Emeritus.

For one who had devoted so much of his busy life to the good of others, it was befitting that during his later years he should be the recipient of numerous honors. At their Sixteenth Meeting in 1941, the Pennsylvania Public Health Association recognized his accomplishments in public health by presenting Dr. Miner with an appropriate scroll. The same organization, seven years later, once more honored him with an award. In 1943, at the conclusion of fifty years in the practice of medicine, Dr. Miner was honored by the Luzerne County Medical Society of which he was a Past-President. In recognition of his contributions to the field of tuberculosis, the Pennsylvania State Tuberculosis Association, at its annual meeting in 1952, cited him and in his honor named after him a ward at the White Haven Sanatorium. He was President of the State Association in 1917 and had been Attending Physician at White Haven. The same group, in 1955 at Pittsburgh, during their Sixty-third Annual Dinner Meeting, honored Dr. Miner and five other former Presidents of that organization.

As a tribute to Dr. Miner's career in the health fields, particularly his leadership in the long, hard fight against tuberculosis, the State Tuberculosis Sanitarium at Hannisburg, Berks County, was renamed, in 1956, the Charles H. Miner State Hospital.

In addition to the various groups already mentioned, Dr. Miner was for many years an active member of the American Medical Association, the Pennsylvania State Medical Society, the State and American Heart Associations, the National Tuberculosis Society and the American Clinical and Climatological Association. In 1923, Dr. Miner became a Fellow of the American College of Physicians. In 1925, during his term of office as State Secretary of Health for Pennsylvania, he was elected an Honorary Fellow of our own College of Physicians of Philadelphia having been a non-resident Fellow since 1917. Dr. Miner was certified by the American Board of Internal Medicine in 1937.

In spite of his exacting medical practice, Dr. Miner found time to carry out with great satisfaction duties on the medical staffs of numerous hospitals. Throughout his life, he never lost interest in the State Tuberculosis

Clinics which he had largely created. From 1897 to 1928, he served well as Chief of the Medical Service of the Wilkes-Barre General Hospital. From 1928 to 1937, he was cardiologist to the same institution. During the latter years of life his activities were largely confined to consultation and private practice in internal medicine wherein he enjoyed the well-deserved reputation as the leading consultant in his field throughout the Wyoming Valley and its surroundings.

It was not only his skill as a physician, but his personality which endeared Dr. Miner to all with whom he came in contact. His quiet, unperturbed manner, along with unfailing dignity and courtesy created in his patients and friends a feeling of security and confidence. Over and above his outstanding contributions to the health of Pennsylvania, Charles Miner was a great and wise physician whose dominating interest throughout his entire professional life was the welfare of those who entrusted themselves to his care. His loss to his community and friends, as well as to his family, is irreplaceable.

Memoir of Louise Pearce (1885-1959)*

By MARION S. FAY, PH.D.

BORN in Winchester, Massachusetts, in 1885, Dr. Louise Pearce was educated in California, first at the Girls' Collegiate School in Los Angeles and then at Stanford University. She studied medicine at Johns Hopkins, receiving her M.D. degree in 1912. After serving as house officer on the medical staff at the Johns Hopkins Hospital for a year, she joined the staff of the Rockefeller Institute for Medical Research as a fellow and was appointed Associate Member in 1923.

Some of her early studies were devoted to the chemotherapy of the spirochetes. She collected a very complete library on syphilis from early manuscripts to modern papers, and bequeathed this collection to the library of the Johns Hopkins Medical School.

Working with Dr. Wade Hampton Brown she investigated the treatment of human trypanosomiasis with tryparsamide. Her monograph published in 1930 reviews the results of ten years, from the first cases treated by her in Léopoldville in 1920 through subsequent field trials by others in the Cameroons and in Equatorial Africa.

But the use of the drug for humans was begun only after a long series of investigations of more than 243 arsenicals in rats, mice and guinea pigs and in rabbits, in which the infection most closely resembled that in man. The pathologists, Brown and Pearce, aided by the chemists, Walter A. Jacobs and Michael Heidelberger, tested a variety of compounds for toxicity and for therapeutic action. The clinical trials in the Congo were carried out by Dr. Pearce. That the woman physician was chosen by the Institute was a tribute to her courage, skill and to her administrative ability. She enlisted the interest and assistance of the local officials in this difficult undertaking. The records and descriptions of the human cases were made with the same meticulous accuracy that was used in the laboratory experiments.

The Belgian government recognized Dr. Pearce's achievement by decorating her with the Order of the Crown. In 1953 after the effects of this work had been observed for more than thirty years, the King of the Belgians made Dr. Pearce an officer of the Royal Order of the Lion and gave honoraria to her and to the other members of the scientific team. It is interesting to speculate on the role of this medical discovery in the present history of the Congo and other African countries.

Further investigations on the use of tryparsamide in syphilis proved fruitful and before the age of penicillin this drug was the preferred agent in the treatment of syphilitic general paresis. These studies led to some unexpected results. The chance discovery in one of the syphilitic rabbits of a malignant tumor was of great importance. This proved to be the first tumor of the rabbit to survive repeated transfers and the Brown-Pearce tumor became an important experimental tool for many laboratories.

In these tumor studies and others made during the work on syphilis and African sleeping sickness, an enormous amount of data on the diseases and constitution of rabbits was accumulated. Dr. Brown outlined a monumental plan to study heredity and environmental effects on these animals from a colony whose history had been carefully preserved. The rabbit colony grew to such large size that housing it became a problem. Also several epidemics of rabbit pox were alarming in their effects, although the purification and identification of the pox virus by

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Dr. Pearce and her assistants brought some good out of this misfortune. The Institute decided to transfer the scientists and their animals to laboratories in Princeton, where housing and chance infections were less of a problem.

Shortly after the move was made, Dr. Brown became seriously ill and thereafter it was Dr. Pearce who had to carry out the program and subsequently to reduce the size and finally to terminate the experiments. With Dr. Harry Greene and several other collaborators she completed valuable studies and published a number of papers. After the Princeton Laboratory was closed and she retired in 1950, she continued to study and edit the data accumulated so carefully over so many years.

Besides her scientific career Dr. Pearce had many other absorbing interests. After moving to Princeton she established her home at Trevenna Farm with Dr. Josephine Baker and the novelist, Ida A. R. Wylie. After Dr. Baker's death, Miss Wylie and Dr. Pearce lived on in the pleasant house, entertaining friends and visiting scientists and writers. The collection of jade and Chinese mementoes collected by Dr. Pearce during 1931–32, when she served as Visiting Professor of Medicine at the Peiping Union Medical College decorated her book-lined study.

Dr. Pearce was an enthusiastic member of the American Association of University Women, serving as a member of the committee for fellowship grants over a number of years. She was vitally interested in education for women and first as a member of the Board and then as President, gave devoted service to the Woman's Medical College of Pennsylvania.

She received recognition of her achievements—many honorary degrees, membership in learned societies, awards and honors. These tokens came to her not only because she was a scientist of stature but because of her personal qualities of courage, forthrightness, kindliness and capacity for friendship.

After she retired, Dr. Pearce and Miss Wylie spent many summers in England or France with a fall visit to Martha's Vineyard. In their summer homes they gave the same generous hospitality that made Trevenna Farm a meeting place for their friends. In 1959 Dr. Pearce became very ill on shipboard when returning home from Europe, and after a brief illness died on August ninth.

Miss Wylie died within two months. One of her last acts was to have the two Belgian medals mounted and framed to hang beside the portrait of Dr. Pearce in the President's Room of the Woman's Medical College of Pennsylvania.

Memoir of William Daniel Stroud (1891–1959)*

By CHARLES C. WOLFERTH, M.D.

WILLIAM DANIEL STROUD, known affectionately to the host of his friends and physicians from one end of this country to the other as Bill Stroud, the son of Morris Wistar and Margaret Rutter Stroud, was born at Villanova in 1891 and died in Bryn Mawr Hospital on August 19, 1959. He was married to Agnes H. Shober in 1923 who with four of their five children, survive him. His many prominent forebearers included Col. Jacob Stroud who founded Stroudsburg.

He attended the Haverford School for 10 years and was graduated from the College of the University of Pennsylvania with the degree of B.S. in 1913. Thereafter he was one of its most loyal alumni. His undergraduate activities included captaincy of the Cross-country Team, membership of Mask and Wig and the Delta Psi fraternity. He was graduated from the School of Medicine of the University in 1916, having spent the summers of 1914 and 1915 working with Sir Wilfred Grenfell in Labrador. This experience fortified Dr. Stroud in his determination to pursue a medical career and won for him the enduring friendship of Sir Wilfred who later in life became his patient. Following internships in the Childrens and Pennsylvania Hospitals, he spent 2 years (1917–1919) in the U. S. Army, including an assignment for training in cardiovascular diseases during which he served under such men as Francis Peabody, Roger Morris and Carl Wiggers. After World War I, he spent a year with Sir Thomas Lewis which led not only to co-authorship of work done together but to a friendship that lasted as long as Sir Thomas lived. He was permitted to work with Sir James Mackenzie on condition that he play golf with his mentor. The young Dr. Stroud hastily bought golf clubs and equipment as a necessary corollary to his scientific training. He also developed an enduring friendship with Sir James, but whether this was because of interest in work, his heroic efforts to furnish Sir James with an interesting golf game or his engaging personality or all three has thus far not been firmly established. He also spent several months at L' Hôpital de Pitié in Paris.

We can mention here only a few of the more important activities, accomplishments, honors received, positions and memberships of Dr. Stroud. He founded the Childrens Heart Hospital of Philadelphia. In 1921, he persuaded Miss Anne Thomson to loan him "The Little White Cottage" where he promptly ensconced 8 children with rheumatic heart disease. The encouragement of Dr. Joseph Sailer and a memorial gift by certain members of the Stroud family helped to keep the movement alive until the magnificent contribution of Mr. William Anderson permitted Dr. Stroud to develop the Hospital toward its present form. He never relinquished membership on its Board. He founded the Heart Clinic of the Pennsylvania Hospital. His active role in the formation of the Philadelphia Heart Association, now the Southeastern Pennsylvania Heart Association and the American Heart Association and his presidencies of both are well known. Perhaps not so well known is the amount of work, energy and enthusiasm he expended upon these now sturdy giants when they were puny infants and their survival was questionable. He stimulated interest in cardiovascular investigation in his friend Edward B. Robinette Jr., and persuaded Mr. Robinette to make a generous gift to the University of Pennsylvania to undertake investigative work

* Read before the College of Physicians of Philadelphia, 4 January 1961. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

in this field. This led to the formation of the Robinette Foundation for research in cardiovascular disease, a pioneer undertaking that owed its origin to the vision and efforts of Bill Stroud as well as the understanding and generosity of Mr. Robinette.

Dr. Stroud was associated throughout his professional life with the School of Medicine and the Graduate School of Medicine of the University of Pennsylvania. In the latter, he long held the position of Professor of Cardiology. He was Consulting Cardiologist to the Philadelphia Lying-In, Pennsylvania, Bryn Mawr, Abington Memorial, St. Christopher's and Norristown State Hospitals in addition to his connections with the Graduate and Childrens Heart Hospitals. He was a Fellow of this College since 1923, an elective councillor 3 years and its Treasurer for 3 years. He was a Trustee of the Hatfield Fund for 24 years and served on the Finance Committee of the College for 8 years, being Chairman 4 years. He was Treasurer of the American College of Physicians for 26 years and upon his retirement from that office the Alfred Stengel Memorial Award was bestowed upon him for distinguished service in behalf of Internal Medicine and especially its cardiovascular branch. He was a member of many other medical societies including the Association of American Physicians, the American Clinical and Climatological Association and the Interurban Clinical Club. He was a member of the Board of Directors of the Philadelphia Tuberculosis and Health Association. He was the author of "Diagnosis and Treatment of Cardiovascular Diseases" now in its 4th Edition, and many papers on cardiovascular diseases. He was a co-editor of Cyclopedia of Medicine in charge of its cardiovascular section.

He served with the First City Troop on the Mexican Border in 1916, became Surgeon to the Troop and subsequently Honorary Surgeon. He belonged to the Sons of the American Revolution. His club memberships included Mask and Wig, Philadelphia Racquet, Gulph Mills Golf, Mill Dam and St. Anthony's of Philadelphia and New York. His business connections were Trusteeship of the Old Green Tree Insurance Company and membership of the Board of Directors of the Western Savings Fund Society of Philadelphia.

Bill Stroud radiated good humor, friendliness and often gaiety, which with his handsome appearance, quick wit and keen but kindly sense of humor, made him extremely popular. He loved verbal fencing with those of his friends who could defend themselves and delighted in a clever riposté. He possessed that mark of a gentleman, consideration for those less favorably situated. He did much to encourage struggling young physicians. He was the soul of hospitality and cemented many friendships among physicians at never to be forgotten dinners given by him. He was beloved by his patients not only because of his obvious interest in them, his wise counsel and ability to inspire hope, but less tangible qualities beyond the ability of this essayist to name, that tend to make us like and trust their possessor. He was a widely sought consultant, the best possible evidence of the regard entertained for ones ability by his fellow physicians.

Although one might never suspect it from even more than casual contact with him, he was a man of deep religious conviction, attended church services regularly and for many years was a vestryman at St. Martins Church, Radnor. His paternal Quaker ancestry and his many contacts with Quakers in his youth may have had much to do with some of the fine qualities he possessed that are so often found in that group. But his father married "out of Meeting" and joined his bride's church. Thus Dr. Stroud was born, as it were, an Episcopalian and remained in that faith throughout his life. To their friends, it seemed that his marriage with Agnes Shober, whose qualities complemented his own so well, turned out to be as perfect as such things can be in this imperfect world.

There is perhaps no more appropriate way to end this memoir than the quotation from John Bunyan sent to Mrs. Stroud by a clergyman friend: "and so he passeth over—and all the trumpets sounded for him on the other side".

Memoir of Myer Solis-Cohen (1877-1960)*

By JESSE T. NICHOLSON, M.D.

MYER SOLIS-COHEN practiced medicine in Philadelphia for nearly sixty years. He was a truly dedicated physician. His devoted concern for his patients, friends and family was matched by his enthusiasm for clinical research, teaching and public health, and his keen interests in patriotism, genealogy, religion and charity.

He was born May 24, 1877, at 1431 Walnut Street, the home of his parents, Dr. Jacob da Silva Solis-Cohen and Miriam Binswanger Solis-Cohen. His father was a pioneer in surgery of the larynx and a founder of the American Otolaryngological Society. He held Professorships at the Jefferson Medical College and the Philadelphia Polyclinic Hospital. His death occurred on January 8, 1960.

Myer Solis-Cohen was the second of eleven children. He attended the Friends Central School, which was then located at 15th and Race Streets. In 1890, he entered Mr. George F. Martin's School for Boys at 39th and Locust Streets. The school's curriculum was based on Mr. Martin's observation at English schools. The annual announcement for the term, 1890–1891 stated, "There is attached to the building, in addition to the large playground, a goodsized exercise hall which gives facilities for gymnastics and winter training in cricket and baseball, as well as for boxing and Indian clubs". Dr. Solis-Cohen's interest in cricket was continued for a number of years as a member of the Germantown Cricket Club. He was also a member of the Logan Tennis Club.

He attended the University of Pennsylvania. His interest in drama was manifested by memberships in the Mask and Wig, and the Garrick Clubs. He also belonged to the Zelosophic Society which was a literary and debating group. He received a Bachelor of Arts degree in 1897, and a Doctor of Medicine degree in 1900. He served his internship at the Jewish and Philadelphia General Hospitals.

His clinical research led to publication of over one hundred medical papers and three popular health books. He contributed greatly to the treatment of tuberculosis, management of communicable diseases, hematological diagnosis, and importance of focal infection in illness. In 1909, he published the first American article on diphtheria carriers. He contributed materially to the early work in the development and use of bacterial vaccines. He spent considerable time investigating bacteriological and possible spirochetal infection as a basis for multiple sclerosis.

Dr. Solis-Cohen held the following teaching positions and hospital appointments; Instructor in Medicine, University of Pennsylvania, Assistant Professor of Medicine, Graduate School of Medicine, Lecturer on Medical Jurisprudence and Toxicology at the Woman's Medical College, Pediatrician to the Jewish and Mount Sinai Hospitals, Eagleville Sanatarium, and the Jewish Maternity, Physician to the Home for Consumptives in Chestnut Hill, and Assistant Physician to the Philadelphia General Hospital. From 1944 to 1951, he was Assistant Director of Public Health for the City of Philadelphia. He was commissioned a Captain in World War I. He served in Base Hospital 59 at Rimaucourt, Hospital 37 at Recey-sur-Ource, and with the 78th Field Artillery in Baigneux as-Juifs. He was commissioned Major in the Medical Reserves in 1925, and Lieutenent Colonel in 1936. Shortly after the United States entered World War II, he again volunteered his

* Read before the College of Physicians of Philadelphia, 7 December 1960. Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

services, but was rejected when his age was ascertained.

It was Dr. Solis-Cohen's great interest in history and genealogy on which he wrote several papers, that led him into matrimony. While attending the meeting of the American Jewish Historical Society, he met Miss Rosebud Teschner, a Doctorate student in History at Columbia University. They were married in 1925. After their daughter, Kathe, was started in her schooling, Mrs. Solis-Cohen took a Doctorate of Philosophy at the University of Pennsylvania.

Dr. Solis-Cohen was a Past President of the Continental Chapter of the Sons of the American Revolution, and the Pennsylvania Society of the Sons of the American Revolution. He was active in the Military Order of World Wars with the title "Surgeon to the Order". He was a member of the Military Order of the Loyal Legion, and the Benjamin Franklin Post of the American Legion.

Dr. Solis-Cohen maintained a lasting interest in his Alma Mater, The University of Pennsylvania. He was regional Vice-President of the Associated University Clubs, and former President of the Philadelphia Society of the Medical Alumni of the University of Pennsylvania. He held a number of other honors in medical circles. He was a former President of the Medical Club of Philadelphia, and also of the Northern Medical Association, a member of the Philadelphia County Medical Society, The Philadelphia Pediatric Society, The Pathological Society of Philadelphia, and The Philadelphia Laryngological Society.

He was sincerely devoted to his religious faith. He stated that while traveling with the Mask and Wig Club for out-of-town performances, he was permitted to leave a day ahead so that he would not break the Sabbath. He was a founder of the Beth-El Congregation, and former officer of the Congregation Mikveh Israel. He was Chairman of the Board of Trustees of the Rothschild Memorial Synagogue.

Dr. Solis-Cohen was a prodigious worker for charitable causes. Most of his professional colleagues will remember the twenty-nine years he served as Chairman of the Committee on Benevolence for the Aid Association of the Philadelphia County Medical Society. They will not forget his untiring efforts to give prompt attention to alleviate the numerous problems that confronted indigent physicians and their families. Cheerfully, he would meet each new challenge that varied from a family recently evicted from its home to arranging for a college scholarship for an orphan. Dr. Solis-Cohen greatly enjoyed the English comedian and actor Albert Chevalier and delighted in singing the songs of Sir Harry Lawder. He loved the Wissahickon. His greatest pleasure was riding or walking along its banks; there, he spent many happy hours on Sundays accompanied by his daughter. Some years after her marriage, he had the great joy of being accompanied by three grandchildren. Sunday excursons extended to the Museums of Science, Art and Natural History, and Historical Shrines. His delight in teaching was only surpassed by the joy of the pupils accompanying him. Here it can well be said that the pleasure which Dr. Solis-Cohen radiated to his fellowmen was exceeded only by their happiness in having him as a companion.

Memoir of David Nathaniel Kremer (1890–1960)*

By TRUMAN G. SCHNABEL, M.D.

DAVID NATHANIEL KREMER, a Fellow of our College for almost forty years, was a native Philadelphian, born on March 28, 1890. He graduated from Central High School in 1907 and was admitted to the University of Pennsylvania in the fall of that year. He received his doctorate in medicine four years later from its Medical School.

He was a Fellow of the American College of Physicians for thirty years and a Diplomate of the American Board of Internal Medicine from the time of its inception in 1937.

He was an active member of the teaching staff of the Department of Medicine at the University of Pennsylvania. His first appointment as Assistant Instructor in Medicine was in 1925, and he rose steadily through the successive ranks to Professor of Clinical Medicine in 1954.

"Dave" Kremer had years of experience at the Philadelphia General Hospital, first as an intern, then as an assistant physician, and finally as a physician with a service of his own. It was in this institution that he spent much time in teaching until 1956 when he was made an Emeritus Professor of Clinical Medicine by his medical *alma mater*. He was also prominently identified with the Doctors' Hospital as a founder, Chief in Medicine, Consultant, and President of its staff from 1953 to 1955. He was an active consultant in medicine at the Oncologic Hospital of Philadelphia from 1953 until the time of his death.

Dr. Kremer wrote a number of papers pertaining to subjects in internal medicine and was highly regarded as a teacher in this field. All thought well of him as a physician and he was frequently spoken of as a "doctor's doctor" by friends and patients.

He married Minna Gabowitz on March 25, 1917. Their marriage was blessed by three children, one of whom, Dr. Howard U. Kremer, is now a Fellow of our College. Dr. David Nathaniel Kremer died on January 29, 1960, and his beloved wife died soon thereafter, on April 19, 1960.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Memoir of George N. J. Sommer, Sr., M.D. (1874-1960)*

By I. S. RAVDIN, M.D.

GEORGE N. J. SOMMER, SR. was born in Trenton, New Jersey, on the 20th of August, 1874, the son of George and Caroline Bender Sommer. He received his early education in the parochial schools of Trenton and the Stewart and Hammond Business College there. For two years he worked with his father as a carpenter, and shortly thereafter entered the University of Pennsylvania School of Medicine from which he graduated in 1894—before the age of 20, contrary to regulations. His class standing was a high one. He interned in the Philadelpia General Hospital and later did graduate work at the Johns Hopkins Hospital in bacteriology. He entered the practice of medicine as an associate of Dr. Elmer H. Rogers in Trenton in 1896 and shortly thereafter became a member of the staff of St. Francis Hospital. It was not long before he was made an assistant surgeon to that hospital, later becoming surgeon, chief surgeon, and finally consultant surgeon, which position he held until his death.

From the time he entered practice in Trenton until 1908 he did both general practice and surgery, but after graduate study in surgery in Berlin he became the first in Trenton to limit his practice to surgery or to any other specialty. He had a special interest in urology for many years, and was a member of, and finally President, of the Philadelphia Urological Society. He also served for several years as Librarian of the Trenton Medical Library and was a member of the Medical Library Association.

He was a member of the American Urological Association, a Fellow of the American College of Surgeons from the time of its founding, and a Governor of that organization for many years. He was a founder member of the American Board of Surgery. In 1930 he became President of The Medical Society of New Jersey. A Fellow of the College of Physicians of Philadelphia since 1935, he attended its meetings over a period of many years. He died on June 20, 1960, after a short illness.

He married Anna C. Murphy who survives him, as do two sons, Dr. George N. J. Sommer, Jr., a surgeon and Fellow of this College, and Thomas Sommer. Dr. Sommer, Sr. exerted a powerful influence, not only in Trenton but in the entire State of New Jersey, for improvement of the standards of medical and surgical practice.

* Prepared and published at the request of the Council of the College of Physicians of Philadelphia.

Report of the Treasurer for the Year Ended November 10, 1960

Assets

General Fund:		
Cash in bank and on hand		$17,312.89
Maintenance and Reserve Fund:		
Cash in bank	$1,023.82	
Investments	11,287.76	
		12,311.58
Miscellaneous Contributions Fund:		
Cash in bank		5,010.82
Library Historical Collections Fund:		
Cash in bank		3,417.41
Trust Funds:		
Uninvested principal cash	13,391.16	
Uninvested income cash (restricted)	31,913.66	
Loan receivable—garage equipment	287.24	
Mortgage	40,500.00	
Real estate	162,746.10	
Bonds	317,945.90	
Preferred stocks	266,065.54	
Common stocks	375,538.15	
		1,208,387.75
Plant Fund:		
Land—15–25 South 22nd Street	95,000.00	
Building	1,420,747.93	
Furniture and fixtures	1.00	
Deposits on perpetual fire insurance policies	11,462.28	
		1,527,211.21
		$2,773,651.66

Funds

General Fund:			
Library general account		$12,182.21	
Library medical documentation service		7,758.63	
Life membership—uninvested funds		877.00	
Reserve for contingencies—uninvested funds		190.02	
Unexpended operating fund balances			
Current operations	($3,616.14)		
Publication committee	(1,133.72)		
President's room	525.00		
Friends of library	20.00		
Books	286.69		
Rare books	152.96		
Campaign expense	145.95		
Portrait	126.47		
Harvey's "De Motu Cordis" Facsimile	(202.18)	(3,694.97)	$17,312.89
Maintenance and Reserve Fund—principal			12,311.58
Miscellaneous Contributions Fund—principal			5,010.82
Library Historical Collections Fund—principal			3,417.41

Trust Funds:			
Principal net worth			
Discretionary common trust fund	1,096,935.09		
Legal common trust fund	24,097.94		
Trust funds not pooled	14,941.06		
Fund for purchase of units in discretionary common trust fund	40,500.00	1,176,474.09	
Income net worth			
Discretionary common trust fund	30,554.56		
Legal common trust fund	831.17		
Trust funds not pooled	527.93	31,913.66	
			1,208,387.75
Plant Fund—principal net worth			1,527,211.21
			$2,773,651.66

NOTES: The various fund investments are shown at their recorded values, which values substantially represent cost.

GENERAL FUND

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

November 11, 1959 to November 10, 1960

Receipts:				
Income on investments, net of agent's fees:				
Trust funds		$72,955.60		
Less:				
Amount transferred to income cash of the several restricted trust funds	$9,808.44			
Erlanger garage expenses paid	6,016.18			
Amount retained in income cash to cover anticipated additional expenses of Erlanger garage	3,840.77			
		19,665.39		
			$53,290.21	
Income funds, principal of which is not administered by the College of Physicians of Philadelphia			1,829.62	
Interest on mortgage			1,885.77	
				$57,005.60
Contributions:				
Fellows dues			58,927.00	
Life membership			1,945.00	
Use of halls and projector			3,101.00	
				63,973.00
Library:				
Contribution plan		16,317.25		
Photostats, fines, etc.		9,575.11	25,892.36	
Medical documentation services			69,896.77	
				95,789.13
Miscellaneous				3,151.35
Total receipts				219,919.08

Disbursements:			
Operating expenses			
Hall committee		$32,993.30	
Office of the Secretary		7,055.26	
Office of the Treasurer		9,427.91	
Pensions		3,177.84	
Campaign expenses		10.00	
Publication committee		6,481.48	
Books		1,678.85	
Entertainment committee		3,231.86	
College collections committee		3,753.65	
Library			
Salaries	$57,712.42		
Books, journals, supplies, etc.	29,210.75	86,923.17	
Medical documentation			
Salaries	27,931.26		
Other expenses	34,206.88	62,138.14	
General funds used to purchase units in Discretionary Common Trust Fund for Pension Reserve Fund		176.58	
			217,048.04
Excess of receipts over disbursements			2,871.04
Add: Cash balance, November 10, 1959			14,441.85
Cash balance, November 10, 1960			$17,312.89

ANNUAL SUMMARY STATEMENT

Statement of Cost of Investment Units Purchased in Discretionary Common Trust Fund by the General Endowment Fund

November 12, 1959 to November 11, 1960

Balance, November 12, 1959		$399,325.12
Receipts:		
Entrance contributions	$2,315.00	
Voluntary contributions from fellows, etc.	1,462.50	
Bequest from Estate of William G. Elmer	500.00	
Book of Remembrance	220.00	
Amortization of mortgage—13th and Locust Streets	2,250.00	
From unit adjustment account	17.44	
	6,764.94	
Deduct:		
Units erroneously issued in prior years on proceeds of amortization of loan on Erlanger garage equipment, already a part of the Fund (46 units)	729.00	
Amount insufficient to purchase one unit, credited to unit adjustment account	11.36	
	740.36	
		6,024.58
Balance, November 11, 1960		$405,349.70

Statement of Cost of Investment Units Purchased in the Various Trust Funds by the restricted endowment funds

November 21, 1959 to November 11, 1960

Discretionary Common Trust Fund		
Balance, November 12, 1959		$624,871.57
Receipts:		
S. Weir Mitchell Associates Journal Fund	$2,800.00	
General endowment for the library	2,018.00	
Life membership fund	685.06	
Pension reserve fund	606.44	
From unit adjustment account (Pension reserve fund)	17.44	
	6,126.94	
Less: Amounts insufficient to purchase one unit, credited to unit adjustment account	39.64	
		6,087.30
Balance, November 11, 1960		630,978.87
Legal Common Trust Fund		
Balance, November 12, 1959 (no change during year)		23,500.00
Trust Funds Not Pooled		
Balance, November 12, 1959 (no change during year)		14,941.06
Total restricted endowment funds, November 11, 1960		$669,399.93

Statement of Cost of Investment Units Purchased in the Discretionary Common Trust Fund by the college extension fund

November 12, 1959 to November 11, 1960

Balance, November 12, 1959		$2,014.48
Receipts:		
Voluntary contributions from Fellows	$517.50	
Income earned on invested principal	95.80	
	613.00	
Less: Amount insufficient to purchase one unit, credited to unit adjustment account	2.82	
		610.48
Balance, November 11, 1960		$2,624.96
Total Funds at book value, November 11, 1960		$1,077,374.59

Jacob H. Vastine, 2nd, M.D.
Treasurer

Annual Report on the Library*

ADMINISTRATIVE

Fiscal Stability

THIS annual report of the College library might well be written by two persons. One reporter could note the advances with pride, while his counterpart could present the alarmist's point of view.

The optimist would emphasize the increasing breadth of the library's base of financial support. The pessimist would note that great advances are needed merely to maintain a research library's relative position in times of rising personnel costs and accelerating flood of scientific literature force-fed by governmental and foundation subsidy.

The Plus Side

The greatest single factor in the College library's favor is the continuing and growing support of a considerable number of individuals and fellow institutions which demonstrate their desire to increase the effectiveness of the library as a collector and disseminator of medical information.

Library Endowment. From the days of its inception in the late eighteenth century, the library has been blessed with the concern of many Fellows who have donated and bequeathed considerable endowments to provide income for library support. Until the time of the second World War this endowment almost produced enough income to meet all of the library's operating costs. Following the war mounting costs outstripped income, and ever increasing demands were apparent to the Follows if the College library was to escape economic malnutrition. During this period an energetic and successful campaign raised about $600,000 to remodel the building and almost to double the library's stack capacity. The bricks and mortar job now completed, the Fellows are devoting major efforts to restoring the endowment to its relatively strong position as an income source.

S. Weir Mitchell Associates. At the first meeting of the Library Committee during the current fiscal year, George I. Blumstein, M.D. was invited to discuss his plan for encouraging endowments for the acquisition and processing of medical journals. Procedural policy and practical details were developed by Dr. Blumstein with the assistance of Richard A. Kern, M.D., the Honorary Librarian, and other members of the Library Committee and Council. By the end of the year the S. Weir Mitchell Associates had been established and twenty-two individual endowments of $1,000 had been given or pledged for the acquisition, binding and servicing of journals. In the bound volumes of the journals identifying bookplates will be inserted, naming the benefactor and any memorial which he may care to indicate. At the end of the year there was reason to trust that many more friends of the College library would choose this way of supporting the library's serials collection.

Contribution Plan—Medical Schools. Commercial institutions have been loyally supporting the College library for more than ten years through participation in the Contribution Plan. This year they were joined on a regular basis by the local medical schools. The Deans' Committee of the five local undergraduate medical schools and the Graduate School of Medicine agreed upon an annual contribution to the College library based upon the number of students enrolled. For the second successive year the College library also received substantial support from the Medical School of the University of Pittsburgh.

This recognition of the economic logic of a strong general research library to augment curriculum materials and specialized research interests of individual schools will undergird the financial strength of the College library.

* 1 November 1959–31 October 1960.

In further recognition of this cooperative relationship, the Fellows of the College revised the regulations which govern the use of the College library by the students of these schools. Borrowing privileges may now be conferred by the Deans of the medical schools or by their authorized representatives. In most cases the Deans have authorized the Librarians of the medical schools to sign library cards for their students.

Contribution Plan—Other non-profit organizations. An increasing number of hospitals and other health agencies are making annual voluntary contributions to help provide a research service to the scientific community. This cooperative approach should ensure the vitality of a central regional research library equipped to provide more library materials and services than any one institution.

Medical Documentation Service. The progress of this fee-for-service arm of the library is given in another section of this report. Note is made here only of the hopeful sign that the Service has passed another milestone in its development by providing, for the first time, an operating margin large enough to begin to offset some of the costs of acquiring and maintaining the necessary literature.

Photoduplication. At the present time the College library is supplying almost as many photocopies in a single month as previously was done in an entire year. A grant from the Smith, Kline & French Foundation made possible the installation of one of the first new Xerox 914 copying machines in this area. One month after its installation in June, it was obvious that speed of operation and improved quality of reproduction led to such an increase in demand that it was necessary to employ a full time operator for the machine. By the end of the report year it was apparent that, with rates lower than those previously charged, an operating margin was being produced which could contribute to the cost of acquiring the original documents which are being copied. It seems reasonable to the library administration to expect the purchaser to contribute to the cost of having the original on hand at the time of his request.

The Minus Side

Despite the encouragement provided by the foregoing, there is much in the library's present position to prevent any smugness. The library staff remains small both by comparison with libraries of similar size and by comparison with its growth in other aspects such as book and journal acquisition. Library salary scales, which have been adjusted upward in each of the last two budgets, still are below rates being offered by many institutions which compete with the College library for personnel.

There has been no recognition on the part of federal fund granting agencies that the College of Physicians Library is an essential resource for the medical research projects which government funds are sponsoring. An informal study was made this year of the reasons for which other institutions were borrowing materials from the College library. In a very high percentage of cases, these loans were being requested on behalf of the holders of government research grants. No percentage whatsoever of these grants is presently allocated by the government for the support of the library which is meeting this need. The regional medical library in a non-teaching educational institution remains unrecognized by federal grant conferring agencies.

Ways have not yet been found to interest the rank and file members of the county and state medical societies in the financial crisis of the independent medical society library with a voluntary membership. Certainly the future development of the profession of which they are a vital part is dependent upon the quality of research and practice. The medical research library is one of the components of the professional complex which must be strong if the whole body of the art and science of medicine is to achieve its greatest potential.

Highlights and Sidelights

Decor. The arrival of six more new chairs in the Reading Room completed the reseating of

this room which was begun last year. Another unit was added to the charging desk which was originally installed two years ago. This addition will hold volumes which are being held for messengers from local institutions which borrow material from the College library. The Smith, Kline & French Foundation grant made this new section possible.

Half Century. The library administration was pleased to be invited to participate in the College's observation of the 50th anniversary of its move into the present building. Fellows and their guests seemed to enjoy the opportunity to inspect the library. The Librarian gave a short talk on possible future developments in the field of facsimile transmission and other mechanical marvels which have promise of applicability to library operations. He emphasized the necessity of maintaining a strong collection of research materials while waiting for these technological dreams to materialize. Historical's role in the evening's program is described in that section of this report.

Cooperative Transfer. Several sizeable collections were transferred to the College library from sister libraries this year. The L. Webster Fox Collection in ophthalmology was transferred from the Franklin Institute. This library of over 400 volumes was given to the College with the consent of Dr. Fox's daughter, Mrs. Beatrice Fox Griffith.

The Academy of National Sciences transferred another 104 medical volumes. This gift was especially important because the College library had an opportunity to screen this collection before the transfer and to take only those volumes which were not already in the library.

The closing of the Preston Maternity Hospital resulted in the transfer of another collection of about 450 volumes of older books in the fields of gynecology and obstetrics. Still another gift of 132 older medical volumes came from the University of Pennsylvania Library.

For the present the College library is unable to do anything but hoard these volumes against some future time when there will be sufficient personnel to process these backlogs and to incorporate them into the collection.

As the year ended arrangements were being made for the transfer of the early homeopathic material from the library of the Hahnemann Medical College.

The reverse of this trend was exemplified by the transfer of the College library's file of *Archives Suisses d'Anthropologie Generale* to the University of Pennsylvania Museum where it is believed it will be in greater demand.

Visitors. Freshman medical classes from Hahnemann Medical College, Temple University School of Medicine and the Woman's Medical College continued the tradition of their annual visits. The library also enjoyed a visit from library interns and new staff members from the National Library of Medicine.

Work simplification. In an attempt to reduce the amount of cataloging work in the library, the cataloging of monographic journal supplements has been discontinued for those journals which are regularly indexed in *Index Medicus.*

The volume of Xerox requests made it desirable to redesign the multiple order forms so that they could serve both as original orders and as invoices after the work has been completed.

Eberhard Foundation. The problem created by the continuing increase in the cost of *Chemical Abstracts* has been alleviated somewhat by the generosity of the Eberhard Foundation which met one half of the cost of this subscription.

Personnel

Miss Joyce Cushmore resigned from the position of Readers' Service Division Assistant which she had held since March 1958. Mrs. Gail Hardesty filled this position from February until June when she left for family reasons. Mrs. Helen Simon held this job from the first of August to the middle of September and was succeeded by Miss Janice Pharr.

Mr. Robert Glass resigned from his position as Library Page at the end of September after serving on the library staff since January 1958. This vacancy was filled by the appointment of Mr. Charles Brown, Jr.

The position of Xerox operator which was newly created in September was filled by the appointment of Mr. William Messner, Jr.

Mr. Jeremy Sweeton and Mr. Anthony Roth were employed on a part time basis during the summer.

Professional Staff Activity. The Medical Library Association is being served by library staff members in the following positions: Miss Muriel Hodge is the Placement Officer and Mr. Elliott H. Morse completed his three year term on the Board of Directors. He also is a member of the Bibliography Committee of the Association.

The library was represented at the annual meeting of the Medical Library Association which was held in Kansas City by Miss Muriel Hodge and Mr. Elliott H. Morse.

An article entitled "Supply and Demand in Medical Literature" by Mr. Morse, appeared in the October 1960 issue of *Journal of the Albert Einstein Medical Center.* The article was based in part on tabulations supplied by Miss Muriel Zeldis. Other professional activities included a lecture in the Postgraduate Course in Medical Writing which was given at the Albert Einstein Medical Center and a lecture on the bibliographic sources in psychiatry for the residents at the Philadelphia Psychiatric Hospital. He also represented the medical society library viewpoint in a panel discussion during the Joint Meeting of the Philadelphia and New York Regional Groups of the Medical Library Association.

Mr. McDaniel's activities are noted in the historical section of this report.

Benefactors. A list of donors of books and other library materials appears in the statistical section of this report.

The library is pleased to be able to report the following institutional subscriptions for the support of the library.

NON-PROFIT INSTITUTIONS

Bryn Mawr Hospital Medical Staff
Graduate School of Medicine of the University of Pennsylvania
Hahnemann Medical College
Harrisburg Hospital
Institute for Cancer Research
Jefferson Medical College
Lankenau Hospital
Philadelphia General Hospital
Temple University School of Medicine
U.S. Naval Hospital Staff, Philadelphia
University of Pennsylvania School of Medicine

COMMERCIAL INSTITUTIONS

Air-Shields, Inc.
Barnes, Dechert, Price, Myers & Rhoads
Beasley & Ornsteen
Bell Telephone Company
Bernstein & Bernstein
Borden Company—Chemical Division
Colgate Biological Laboratories
Dentists' Supply Co.
Dilworth, Paxson, Kalish, Kohn & Dilks
E. I. du Pont de Nemours, Haskell Laboratory
E. I. du Pont de Nemours, Lavoisier Laboratory
E. I. du Pont de Nemours, Stine Laboratory
S.F. Durst & Co.
Eaton Laboratories
Jerome Edelman
Freedman, Landy & Lorry
General Atronics Corp.
General Electric Co., Missiles & Ordnance Systems Dept.
Gray & Rogers
Halbert & Kanter
Harvey & Thomas
Institute for Scientific Information
Kontes Glass Co.
La Wall & Harrisson
Lee Ramsdell & Co.
Lewis & Gilman, Inc.
MacAndrews & Forbes Company
McNeil Laboratories
Mead Johnson & Co.
Merck Sharp & Dohme
Morgan, Lewis & Bockius
Mulford Colloid Laboratories
National Drug Company
Norwich Pharmacal Co.
Oxy-Catalyst Inc.
Pennsylvania Railroad Company
Chas. Pfizer & Co. Inc.
Prudential Insurance Co.
Quaker Chemical Products Corp.
Richter, Lord & Levy

Rittenhouse Book Store
A. H. Robins Co. Inc.
William H. Rorer
Rohm & Haas Company
Schnader, Harrison, Segal & Lewis
Scientific Literature Inc.
Smith, Kline & French Laboratories
E. R. Squibb & Sons
Arthur H. Thomas and Company
Wallace Laboratories
Warner-Lambert Laboratories
Williams & Wilkins Co.
Wyeth Laboratories

E. H. M.

Historical

The Historical Cataloguing Project referred to in our latest two reports continued in operation throughout the period covered by the present report, and naturally exerted a centripetal force on the curator's normally untidy operations. By 1 December 1960, when the Project came to a premature, temporary halt, for a premature reason, Mrs. Maria A. Shchuka, the cataloguer, and her successive assistants, Mr. Lev Revucky, Mrs. Susanna B. Quinn, and Miss Hildegard Gutzmann, had made available for use 749 historical items (involving the typing of 9,603 catalogue cards) that had been awaiting cataloguing for periods ranging up to a decade and more. Gratifying as this is, and grateful as we are to the American Philosophical Society for making it possible, it is but a token of what remains to be done to put our historical domus in order. There is still a large accumulation of valuable, potentially useful, uncatalogued material about—and more comes in almost daily. The funds still available for the present project will permit its extension, when it can be resumed, for another two or three months only. It is clear that, if the rich historical resources presently at hand are to be fully processed for use, and the steady stream of additions expeditiously dressed for the street, "Think big" must be the order of the day for all those who would wish the collections to continue casting their traditional healing beam on a naughty world. At the risk of wearying the converts, but in clear line of duty, it must be reiterated that a permanent staff of one is inadequate for responsible handling of the complex demands on a large and multifaceted historical collection that is still in process of growth.

Elsewhere in these pages will be found a supplement to the 1938 *Census of Incunabula* in the library. In it is listed an acquisition of the past year: Jean Ganivet's *Amicus Medicorum* [Friend of Physicians], Lyon, 1496—characterized by Thorndike as probably the most influential treatise on astrological medicine composed in Europe in the 15th century. This is the first edition; Stillwell's *Incunabula in American Libraries* (1940) lists but a single copy in the U.S., Mexico, and Canada, that one being at Harvard. As indicated above, there were numerous other important acquisitions of later date. And, again, the larger number of these were donated, or their purchase made possible, by Fellows of the College and various *amici medicorum*; in the former category, with notable frequency, Drs. Fred B. Rogers and J. Monroe Thorington, and the corporate Section on Medical History.

As last year, nine issues of the *Fugitive Leaves* were given to the winds. Nos. 33–35 presented two manuscript letters (the authorship of one had just been identified) written by Charles D. Meigs to René La Roche, both prominent 19th century Philadelphia physicians; Nos. 36–40 contained historical notes on the College's eight eponymous lectureships; No. 41, some hitherto unknown doggerel rhymes, in manuscript, on Philip Syng Physick, found in material donated by the family of S. Weir Mitchell.

For the commemoration of the 50th anniversary of the dedication of the College's present building, 10 of the College's 49 American *incunabula unica* (according to Stillwell) were displayed, all acquired since the building was opened. Other exhibits, in addition to the programatic ones provided for the Section on Medical History, were devoted to: 1) annual

announcements of early American medical schools; 2) illustrations in incunabula; 3) early medical bibliographies and bio-bibliographies. It is hoped that the lighting of the exhibit cases—a source of vexation to many would-be viewers—may be improved in the near future.

The curator had the pleasure of demonstrating some of the numerous types of useful historical material at the final meeting of the Drexel Institute's first course in medical bibliography; and of giving a brief talk at the dinner held in connection with the 50th anniversary celebration mentioned above. He continued to serve on the Osler Medal Committee of the American Association for the History of Medicine.

W. B. McD., 2d

Medical Documentation Service

The past fiscal year has been one of continued healthy expansion in the activities of the Medical Documentation Service. As our circle of friends continues to widen, varied requests for bibliographical assistance have been received from far corners of the nation and at the same time, a growing number of physicians and research workers in the Philadelphia area has become more aware of what the Service offers. Thus, while gaining such major new clients as the American Institute of the Biological Sciences, for whom an annotated bibliography on influenza is in preparation, we have also expanded our services to such old friends as the National Foundation, and have added a large number of new names, both commercial and individual, to the list of clients for whom our specialized scanning, abstracting, translating and literature searching activities are performed. Among the special projects engaged in during the year have been continued abstracting for Biological Abstracts and the Cancer Chemotherapy National Service Center of the National Institutes of Health, and the preparation for publication of the proceedings of the 1959 meeting of the Inter-Society Cytology Council.

Concomitant with the continued expansion of activities, there have been a number of changes in the M.D.S. staff. Early in the year, the Service acquired a full-time assistant director in the person of Dr. Walter Bethel, who had been employed for some time on an hourly basis, and as the year ended, plans were being made to employ Dr. Robert Asnis on a permanent basis as staff bibliographer. During part of the spring the Service enjoyed the assistance of Mr. Cyrus Sturgis in the cancer chemotherapy abstracting project. Mrs. Jean Stevens continues in her capable role of executive secretary, assisted during the year by a number of parttime employees, including Mrs. Margaret Holloway, Mrs. Kathleen Miller, Mrs. Margaret Dardis, Miss Joan Cantor and Miss Joan LeVere. As the year ended, however, Dr. Blanken was preparing to relinquish the post of director he had held since 1958, Dr. Bethel was in the process of promotion to director.

Statistically speaking, the Service scanned the literature for an average of 29 subjects during the year, reporting a total of 9162 references to about 20 clients; this compares with 5618 references during the previous fiscal year. During 1959–60, the Service also prepared 5642 abstracts, 193 bibliographies and 140 translations.

Financially, this activity is reflected in a gross income of almost $70,000, compared to $50,000 in 1958–59, more than half (60%) of which came from abstracting, with other large contributions from the scanning service ($11,000), literature searching and translating ($6,000). This income is not quite balanced by expenditures of about $61,000, including $26,000 in wages and $26,500 to abstractors and translators. The operating margin will help defray overhead costs and expenses which are not included in the major budget categories mentioned above. It should also be mentioned that the expenditures include the acquisition of a certain amount of new equipment, in-

cluding office furniture and a Recordak microfilm camera which is now the property of the library.

The continued growth of the Medical Documentation Service and the success in balancing the budget certainly augurs well for the fiscal year 1960-61.

R. R. B.

STATISTICAL SUMMARY

Inventory

	1960		1959	
Accessioned items[1]				
Incunabula[2]	420		419	
Manuscripts and typescripts	938		936	
General	202,942		198,995	
Accessioned pamphlets	4,628		4,508	
		208,928[3]		204,858
Unaccessioned items[1]				
Reports	28,794		28,793	
Theses	60,158		59,763	
Pamphlets and reprints	231,472		231,458	
		320,424		320,014
Portraits[4]		103,828		103,221

Current Serials

	Subscription	Gift	Exchange	Total
U.S.A.	347	400	65	812
Western European Continent	634	65	129	828
Latin America and West Indies	13	74	65	152
United Kingdom and Eire	121	29	30	180
Canada	8	14	8	30
Eastern European Continent	45	33	28	106
Asia (including Japan)	18	60	57	135
Africa	1	6	14	21
Pacific (including Australasia)	3	13	9	25
United Nations	10	—	—	10
International	19	7	—	26
Grand Total: 1960	1,219	701	405	2,325
Grand Total: 1959	1,153	696	416	2,265

[1] Accessioned items in this library comprise the total number of bound volumes and such unbound pamphlets as have been catalogued as separate bibliographical units regardless of their size.

There remain many thousands of unaccessioned pamphlets awaiting accessioning and cataloguing. A true quantitative and qualitative picture of the library's holding cannot be presented until this wealth of neglected material has been processed and duly registered in our 'accessioned', or 'volume', count.

[2] The library owns 422 incunabula but there are two cases of two bound together, reducing the number of accessioned items.

[3] Included in this figure are the following collections which are on permanent deposit in the library: Gross Library, 3,976 accessioned and 4 unaccessioned items; Parry Library of the Obstetrical Society of Philadelphia, 217; Mütter Museum, 200 (Mütter Museum books may not be removed from the College building).

[4] Including 124 oil, and 268 other, framed portraits in the care of the Committee on College Collections. The count of portraits represents the number of entries on the cards in the portrait catalogue. The entries represent, in turn, both loose portraits and those in books, many of them, of course, being merely different reproductions of a single original.

New titles: A total of 96 serials was added in 1959–60.

Separate Issues received, checked-in on the cards, and shelved totaled 19,863. In addition, thousands of duplicate issues were received as usual. No attempt was made to count those held merely for exchange or other use.

Visitors in the Norris Room for the year totaled 3,407.

Readers' Use of the Library

Library Hours. The library was open, during the academic year, from 9:30 to 9:30 on Mondays and Wednesdays, from 9:30 to 5:30 on the other weekdays. During June, July, August, and the first half of September the library was open from 1 to 9:30 on Tuesdays; from 9 to 5 on the other weekdays, except Saturdays, when it was closed. The following legal holidays were observed: Thanksgiving, Christmas and New Year's, Memorial, Independence, and Labor Days.

Visitors:

	Totals
1960:	9,694
1959:	14,109

Circulation:

	Totals	*Intra-mural*[6]	*Extra-mural*[6]	*Books*	*Journals*
1960:	63,181	45,792	17,389	12,010	51,171
1959:	59,294	44,381	14,913	11,962	47,332

Inter-library loans: The library sent 13,359 (1959: 9,161) volumes on inter-library loan to 91 (1959: 177) libraries in 35 (1959: 26) States including Washington, D. C., and Canada and has borrowed 15 (1959: 13) volumes from 4 (1959: 3) libraries.

Photoduplications: 19,357 photoduplications were furnished on request (1959: 5,836)

Accessioned Acquisitions:

1960: 4,070 volumes (1,957 by purchase; 1,697 by gift; 416 by exchange). (Books: 1,264; Periodicals: 2,686; Pamphlets: 120).

1959: 4,143 volumes (2,052 by purchase; 1,674 by gift; 417 by exchange). (Books: 1,312; Periodicals: 2,738; Pamphlets: 93).

Non-accessioned Acquisitions:[7]

1960: 1 Report (1959: 2)
395 Theses (1959: 242)
62 Miscellaneous items (1959: 9)

Donations

The donors for the past year number 129 (1959: 105). The library is indebted for large gifts of books, pamphlets and unbound periodicals to the following donors: Academy of Natural Sciences of Philadelphia; Children's Hospital; Franklin Institute; Hahnemann Medical College; Hospital of the University of Pennsylvania; Institute of the Pennsylvania Hospital; Jefferson Medical College; Dr. R. A. Kern; Lee Ramsdell; Mercy Douglass Hospital; National Drug Co.; Dr. G. W. Norris; Dr. A. H. Persky; Smith Kline & French; Temple University; Valley Forge Army Hospital; Veterans Administration Hospital; Wistar Institute; Woman's Medical College.

Various publishing houses, among the large group of corporate donors, have presented volumes as follows: F. A. Davis Company, 7; Lea & Febiger, 10; J. B. Lippincott Co., 30; W. B. Saunders Co., 77.

Other individual donors were as follows: Drs. F. H. Adler; H. A. Arkless; O. V. Batson; S. Bellet; E. W. Bixby; M. W. Brody; T. Cianfrani; I. S. Cohen; P. C. Colonna; J. Dankmeijer; J. M. Deaver; Miss E. Diuguid; Drs. G. G. Duncan; C. B. Farr; L. Flinkman; J. T. Freeman; J. F. Fulton; J. Gershon-Cohen; T. S. Githens; R. P. Glover; S. B. Hadden; C. A. Hatfield; Miss C. D. Hellman; Dr. H. Hinkson; Miss C. J. Jones; Drs. J. Kirsch-

---

[5] The number of volumes "consulted in the library" includes only those supplied on demand. Readers have access to the bound volumes of periodicals and reference works kept on the shelves in the Reading Room; the Fellows, and occasionally others, by special permission, have access to the book-stacks. There are, therefore, many volumes consulted of which no accurate record can be kept.

[6] This figure includes 4,293 unbound current issues circulated from the Periodicals Room.

[7] As usual, not all the pamphlets, theses, and numbers of various journals listed as received have been checked for keeping or discard at the close of the library year.

baum; J. V. Klauder; N. L. Knipe; E. B. Krumbhaar; Mrs. I. Langman; Mr. L. Lebman; Drs. J. J. B. Light; F. D. W. Lukens; S. N. McCann; Mr. W. B. McDaniel, 2d.; Drs. C. Macfarlane; H. Maibach; E. A. Mallon; M. Naide; G. W. Norris; D. M. Pillsbury; H. Robertson; F. B. Rogers; H. R. Rollin; J. B. Rudolphy; W. J. Ryan; L. C. Scheffey; T. G. Schnabel; D. M. Schullian; E. Shearburn; W. B. Shelley; L. Solis-Cohen; I. Starr; Mrs. A. G. B. Steel; Dr. J. A. Sterling; Mrs. W. D. Stroud; Mrs. Sutro; Drs. J. M. Thorington; J. T. Ullom; Miss H. N. Wilson; Mr. E. Wolf, 2nd; Drs. I. J. Wolman; W. C. Yakovac.

The Transactions & Studies was sent, either in exchange or as gift, to 500 organizations.

Theses and dissertations to the number of 391 have been received on exchange from the following European schools of medicine: Universities of Basel, Bern, Copenhagen, Djakarta, Erlangen, Geneva, Leiden, Louvain, Lund, Uppsala, Utrecht.

THE STAFF[8]

Librarian
Elliott H. Morse

Assistant Librarian & Cataloger
H. Muriel Hodge

Serials Librarian
Muriel Zeldis

Serials Assistant
Dorothy Minton

Circulation-Reference Librarian
Mrs. Elnora Smith

Readers' Service Division Assistant
Janice Pharr

Order Librarian
Mrs. Kathryn E. Miragliotta

Cataloging Assistant
Mildred C. Gray

Library Secretary
Mrs. Dolores McFadden

Curator of the Library's Historical Collections
W. B. McDaniel, 2d, Ph.D.

Medical Documentation Service
Walter L. Bethel, Ph.D., Director
Robert E. Asnis, Ph.D., Staff Bibliographer
Mrs. Jean C. Stevens, Executive Secretary

Pages
Catherine Ledwell
Philip Ballinghoff
Daniel Cavanaugh, Jr.
William Messner, Jr.
Charles Brown, Jr.

Approved:
JOHN FRANKLIN HUBER, M.D.
Chairman, Library Committee

---

[8] Library staff list as of January 1, 1961.

Annual Report of the Committee on the Mütter Museum and College Collections

ALTHOUGH to many the Mütter Museum of the College of Physicians often seems deserted, there were actually 1901 visitors during the year 1959–1960. The museum is open daily except Saturdays and Sundays from 9.30 A.M. to 1 P.M. and from 2 P.M. to 4 P.M. Although it is closed for the lunch hour between 1 P.M. and 2 P.M., visitors who come in groups may also gain entrance at this hour by previous arrangement with the curator. On the stated monthly meetings of the College the curator is in attendance until 8.30 P.M.

In recent years the attendance has been increased by the number of classes from medical, public and private schools who come to visit the museum and the library. Although we had fewer visitors from foreign countries this year, there have been larger classes from Hahnemann Medical College, Woman's Medical College, Temple University School of Medicine, and some of the public schools.

Student nurses and those who are already practicing as graduate nurses, find the exhibits helpful and interesting; large groups of them came from Villanova College and the Montgomery Hospital in Norristown. Other schools represented were Radnor High School, Clifton Heights High School, St. Leonard's Academy and the Franklin School of Science and Arts. Interest varies in the different groups from the public schools, and even in different classes in the same school from year to year. For that reason we have tried to discourage visits from those who are not particularly interested, but merely curious, or who are too immature to appreciate the information the exhibits offer.

An amusing and informative article on the Mütter Museum written by Mr. James Smart of the Evening Bulletin, appeared in that paper one evening under the heading "In Our Town." This attracted many intelligent and interested non-professions visitors.

The museum was able to be of service to a biographer of Dr. Joseph Leidy, Dr. D. H. Wenrich, by supplying him with a photograph of the death mask of Dr. Leidy which he wished to use as an illustration in his book.

Dr. Samuel X Radbill brought his post-graduate class in pediatrics from the University of Pennsylvania to the museum as he does every year, where they were shown many of the items in the museum that are of particular interest to a pediatrician. Dr. Radbill also brought many of the feeding bottles and dishes in his own collection, explaining their origin and time of use. Of particular interest was a crude one of metal, evidently hand-made.

Dr. John B. Blake, Associate Curator in the Section of Medical and Dental History in the Department of Science and Technology at the Smithsonian Institution, who visited the museum several times, asked permission to have a copy made of one of the Ambroise Paré instruments for his department. This was granted and Mr. L. C. Eichman of Clifton Heights, New Jersey, came to the museum and made the cast.

The 72nd Thomas Dent Mütter Lecture was delivered on February 3, 1960 by Paul E. Steiner, M.D., Professor of Pathology at the University of Pennsylvania and Senior Member of the Institute for Cancer Research. The title of the address was "*Etiology of Human Liver Cancer in Africa and the United States.*"

All accessions received this year were catalogued under College Collections so that they may be loaned for any worth-while purpose upon request, although displayed in the Mütter Museum.

Mrs. Ella N. Wade was reappointed curator for the year 1960–1961.

College Collections

Because several of the oil portraits in the collection have been damaged by falling from

the wall because of loose hooks or old wire, necessitating expensive repairs, on the suggestion of Mr. Frank Ireland, the artist, Council voted to have them all rewired and supplied with double hooks. So far this has been done on all but four of the portraits, by Mr. Allen and the janitorial staff.

During the year Mr. Ireland restored and repaired the portraits of Drs. James Hutchinson, Charles Thomas Hunter and William Thomson.

A photograph of the Paul Ehrlich Medal was sent to the University of Wisconsin upon request, and copies of the Medical Medal Catalogue were sent to those requesting them, one of which went to Professor K. F. Russell in the Department of Anatomy at the University of Melbourne, Australia.

The Florence Nightingale sewing kit which she used while in service during the Crimean War was loaned to the Free Library for exhibit in connection with "Careers in Nursing," and it is reported to have added to the interest of the exhibit.

The items in College Collections were increased considerably during the year.

Dr. Fred B. Rogers, a generous donor, presented the College with a number of instruments and articles formerly belonging to his father, Dr. Lawrence H. Rogers, and his great-uncles, Drs. Elmer H. Rogers and Benjamin H. Rogers. These were, namely, a Nicholson's "Princo" Sphygmomanometer, a fine nineteenth-century surgical kit, two pairs of obstetrical forceps, a set of Lee metallic splints, an abdominal trocar, and a cane given to his father upon graduation from New York University College of Medicine in 1908.

Besides, *Dr. Rogers* donated a caricature of Dr. Oliver Wendell Holmes by Spy, a colored engraving of Dr. Richard Mead, a bronze medal of Laennec by Albert Herbemont, and a shoulder patch of the Italian Red Cross Volunteer Hospital Unit in the Korean War, 1950–53.

Dr. Edward F. Corson, who has given the College so many British War Medals, added two more to the collection, and *Dr. Samuel X Radbill* presented an old pair of obstetrical forceps.

The College was presented with two apothecaries' scales, one from *Dr. Norman L. Knipe*, the other from *Mrs. George W. Norris*. This had formerly belonged to Mrs. Norris' grandfather, Dr. Isaac Hays, a former Fellow of the College.

Mrs. Thomas Francis of Radnor received permission from the College to photograph the charcoal drawing of Sir William Osler, by John Singer Sargent (1914), in the College portrait collection, which she wished to present to Dr. Wilder G. Penfield, neurosurgeon at McGill University, in appreciation for the treatments he gave her daughter who is afflicted with encephalitis. Mrs. Francis had an extra print made which she had framed and presented to the College.

The Wood Room of the College now has on its walls a framed Certificate of Membership in the College of Physicians issued to Dr. Horatio C. Wood in 1865. This was presented by *Mrs. Horatio C. Wood Jr.* in memory of her husband, Dr. Horatio C. Wood, Jr.

O'Hara's anastomosis forceps invented by Dr. Michael O'Hara, Jr. (1869–1926) were given by his daughter, *Miss Constance O'Hara*.

The interesting phlebotomy instrument collection was increased by one spring lancet donated by *Dr. Carl C. Fischer*.

Dr. Douglas Macfarlan, another generous donor, always looking for new hearing aids to bring that collection up to date, this year interested *Mr. Irving I. Schachtel*, President of the Sonotone Corporation, in the rapidly growing collection, with the result that *Mr. Schachtel* added six more hearing aids of fairly recent manufacture. Among them is an older model, a carbon type bone conduction instrument dated 1930, which made it possible to hear amplified sounds through the bones of the head instead of through the impaired pathways at the outer and inner ear.

Model 966 (1951) is the "first" ultra power wearable hearing aid, and model 1010 (1952) is the "first" hearing aid to use the transistor instead of the vacuum tube.

Other "firsts" are model 79 (1956) the first behind the ear aid with all the parts contained in one compact unit, model 222 (1957) the smallest aid containing three transistors, to be worn entirely in the ear, and model 410 (1958), an eyeglass aid first to incorporate the exclusive Sonotone automatic control feature.

Thanks to *Dr. Macfarlan* and the manufacturers and dealers he has interested in the collection, the hearing aid exhibit from the ancient ear trumpet to the present aids is the most complete in the College or Museum collections.

Dr. Macfarlan also presented to the College a small bust of Dr. Albert Schweitzer by Louis Michelotti, made in 1959.

A framed drawing of Dr. S. Weir Mitchell, by George T. Tobin, was given by the *Section on Medical History.*

Mrs. Ella N. Wade was reappointed clerk-technician for the year 1960–1961.

A. Reynolds Crane, M.D.
Chairman (protem)

Census of Incunabula in the Library of the College of Physicians of Philadelphia, 1938. Supplement 1, 1960

Foreword

SINCE the last census of incunabula in the College library was published, in 1938,[1] the population in this district has increased by fourteen. The vital data on only a few of these 15th century immigrants have been recorded in the library's published reports. It is thought, therefore, that a supplement to the 1938 census, bringing the record completely up-to-date in a single place, would prove useful.

For the sake of consistency, this supplement follows the general policies laid down in the foreword to the 1938 census. The primary references are to Klebs's *Incunabula Medica et Scientifica* (1938), which lists all but two of the editions recorded below; and to Stillwell's *Incunabula in American Libraries* (*Second Census*) (1940), which lists all but three of them. Though these sources give references to the standard general bibliographies of incunabula, we have again also included, as first-aid to those not having ready access to the specialized Klebs and Stillwell. references (when possible) to the standard Hain-Copinger-Reichling (HCR), British Museum Catalogue (BMC), and, lamentably still far from complete, Gesamtkatalog der Wiegendrucke (GW).

W. B. McDaniel, 2d[2]

[1] Census of incunabula in the library of the College of Physicians of Philadelphia, 1938, *Trans. & Stud. Coll. Phys. Phila.*, 4th ser., **6**: 159–193, Sept., 1938.

[2] Curator, Library Historical Collections. The 1938 census was published anonymously. Its compiler, the present supplementer, was, at the time, privately reprimanded by an admired friend, the late Dr. John F. Fulton, for having allowed personal reticence to take precedence over proper acknowledgment of responsibility. Sympathetic, but not always faithful, to the valid precept since then, the census-taker finds it personally obligatory to be faithful in the present instance.

The Incunabula

Eschuid, Johannes [Estwood, John]

Summa astrologiae judicialis. Venice, Santritter for Bolanus, [7 July] 1489.

Klebs 381.1; Stillwell E84; HC 6685; BMC v, 462; GW 9392.

Ganivetus, Johannes

Amicus medicorum [et alia opuscula]. Lyons, Trechsel, 14 Oct. 1496.

Klebs 436.1; Stillwell G63; HC 7467.

Gentilis Fulginas

Consilium contra pestilentiam. [N. pl., pr., d.]

Klebs 445.2 [Colle, 1478]; Stillwell G123 [Bonus Gallus, about 1479]; R 530 [ca. 1480]; BMC vii, 1079 [Colle; Gallus].

Guido de Cauliaco

[*Chirurgia*] [in Italian]. Venice, P. de Quarengiis & G. M. Occimiano, 21 Aug. 1493. [Bound with the Guilelmus de Saliceto, below.]

Klebs 492.2; Stillwell G516; HR 4817; BMC v, 511.

Guilelmus de Saliceto

[*Chirurgia*] [in Italian]. Venice, N. de Ferrariis, 16 Feb. 1491. [Bound with the Guido de Cauliaco, above.]

Klebs 485.3 [16 Dec.]; R 718.

Manfredis, Hieronymus de

De peste. [N. pl., pr., d.]

Klebs 656.1 [Bologna; 1482?]; Stillwell M169 [Bologna, Joh. Walbeck, after 31 Dec. 1479]; HR 10696 (R vi, 94) [Bologna, Valbeck, c. 1480].

Pantaleo de Confluentia

Pillularium. [N. pl., pr., d.]

Klebs 720.1 [Pavia, a. 17 Feb. 1484]; Stillwell[3] P68 [Pavia; n. pr., n.d.]; R 1601 [Pavia, Antonius Carcanus, c. 1480].

[3] The single copy of the work listed in Stillwell is now known to be a fragment of a 16th century printing of it.

Pintor, Petrus

De morbo fedo & occulto [de morbo gallico]. Rome, Silber, 9 Aug. 1500.

Klebs 780.1; HC 13010.

Salicetus, Nicolaus

Antidotarius animae. Strassburg, J. (Reinhard) Grüninger, [4] March 1494.

Stillwell S39; HC 14164 (date appearing as 'Mccccyciij').

Scriptores rei militaris. Bologna, F. P. de Benedictis, I) 10 July 1495; II) 16 Nov. 1495; III) [n.d.]; IV) [n.d.]; I–IV) [17 Jan.] 1496.

Klebs 903.3; Stillwell S317; C 5330; C 2594.

Valle Robertus de [Duval, Robert]

Compendium memorandorum Plinii. Paris, Baligault for Gerlier, 1500.

Klebs 357.1; Stillwell V71; HC 15836.

Villardiga, Antonio

Juyzio . . . para el año de M.D. [y de M.D.j y ij]. [N. pl., pr., d.]

Vindel, F. El arte tipográfico en España durante el siglo XV; Salamanca etc., no. 129. Madrid, 1946.

Vincentius Bellovacensis

Speculum doctrinale. Nuremberg, Koberger, [16 March] 1486.

Klebs 1037.2; Stillwell V251; C 6243.

Widman, Johannes[4]

De pestilentia. [Contains also: **Biel, Gabriel.** *Fuga pestis.*] Tübingen, [anon. pr.] for F. M., [n.d.].

Klebs 1049.1 [Frid. Meynberger, 1501]; Stillwell W13 [Johannes Otman for Friedrich Meynberger, after 1500?].

---

[4] The propriety of including this imprint so belatedly (the library's copy was accessioned in 1901) is questionable. The chief reason for doing so is the fact that Stillwell includes it.

Transactions of the Sections

SECTION ON GENERAL MEDICINE

22 February 1960

THE USE OF GUANETHIDINE (ISMELIN) IN THE TREATMENT OF HYPERTENSION. John G. Kelly, M.D.*, Edmund L. Housel, M.D., and James W. Daly, M.D.* (Discusser: Albert N. Brest, M.D.*) (*Abstract 1*, below)

CYCLOPHOSPHORAMIDE IN THE MANAGEMENT OF MALIGNANT DISEASE. Sylvan H. Eisman, M.D.*, Robert G. Ravdin, M.D., and Peter F. Coggins, III, M.D.* (Discusser: George C. Lewis, Jr., M.D.*) (*Abstract 2*, below)

OPEN HEART SURGERY FOR MITRAL STENOSIS AND MITRAL REGURGITATION. Henry T. Nichols, M.D., Gumersindo Blanco, M.D.*, Joseph F. Uricchio, M.D., and William L. Likoff, M.D. (Discusser: Charles K. Kirby, M.D.*) (*Abstract 3*, below)

THE HEART IN GLYCOGEN STORAGE DISEASE. Otto F. Muller, M.D.*, and Samuel Bellet, M. D. (Discusser: William E. Ehrich, M.D.) (*Abstract 4*, below)

28 March 1960

ALVEOLAR HYPOVENTILATION DUE TO INVOLVEMENT OF THE RESPIRATORY CENTER BY OBSCURE DISEASES OF THE CENTRAL NERVOUS SYSTEM. Theodore Rodman, M.D. (Discusser: Elliot L. Goodman, M.D.*) (*Abstract 5*, below)

POSTGASTRECTOMY STEATORRHEA—ITS RELATIONSHIP TO AFFERENT LIMB STASIS AND BACTERIAL FLORA. Franz Goldstein, M.D.*, C. Wilmer Wirts, M.D., and Simon Kramer, M. D.* (Discusser: George J. Haupt, M.D.*) (*Abstract 6*, below)

PNEUMATOSIS CYSTOIDES INTESTINALIS: REPORT OF TWO CASES. Lucy J. Balian, M.D.*, Allen J. Steinberg, M.D.*, and Burton Schaffer, M.D.* (Discusser: John W. Hope, M.D.*) (*Abstract 7*, below)

STUDIES ON PULMONARY OSTEOARTHROPATHY. H. Edward Holling, M.D.*, Robert S. Brodey, D.V.M.*, and H. Christine Boland, B. S.* (Discusser: Robert L. Mayock, M.D.) (*Abstract 8*, below)

25 April 1960

COMPARATIVE BIOASSAY OF DIURETICS, Morton Fuchs, M.D.*, and John H. Moyer M.D. (Discusser: Edward J. Huth, M.D.*) (*Abstract 9*, below)

EFFECTS OF FAT UPON CORONARY AND PULMONARY CIRCULATIONS: AN EXPERIMENTAL STUDY. Peter T. Kuo, M.D.*, Arthur F. Whereat, M.D.*, Arthur A. Altman, M.D.*, and James W. West, Ph.D.* (Discusser Joseph H. Hafkenschiel, M.D.) (*Abstract 10*, below)

EXPERIENCES WITH INHIBITORS TO THE PLASMINOGEN-PLASMIN SYSTEM IN MAN. George Tsitouris, M.D.*, Herschel Sandberg, M.D.*, and Samuel Bellet, M.D. (Discusser: Brooke Roberts, M.D.) (*Abstract 11*, below)

CHRONIC CHOLECYSTITIS: INDICATIONS FOR REVISION OF THE CLINICAL DIAGNOSIS. Edwin L. Lame, M. D. (Discusser: Howard P. Potter, M.D.*) (*Abstract 12*, below)

23 May 1960

DELIRIUM TREMENS: AN ANALYSIS OF FATALITIES OCCURRING AT THE PHILADELPHIA GENERAL HOSPITAL IN A NINE-YEAR PERIOD. Morton E. Tavel, M.D.*, Warren Davidson, M.D.*, and Thomas D. Batterton, M.D.* (Discusser: Charles M. Thompson, M.D.) (*Abstract 13*, below)

IDENTIFICATION OF URATE CRYSTALS IN GOUTY SYNOVIAL FLUID. Daniel J. McCarty, M.D.*, and Joseph L. Hollander, M.D. (Discusser: George D. Ludwig, M.D.) (*Abstract 14*, below)

HYPONATREMIA AND RENAL SODIUM WASTING IN PATIENTS WITH MALFUNCTION OF THE CENTRAL NERVOUS SYSTEM. Martin Gold-

* By invitation.

berg, M.D.*, and Joseph S. Handler, M.D.* (Discusser: Earl S. Barker, M.D.*) (*Abstract 15*, below)

Ganglion Blocking Agents Used in Combination with Rauwolfia and Chlorothiazide for the Treatment of Hypertension. Albert N. Brest, M.D.*, and John H. Moyer, M.D. (Discusser: Alfred M. Sellers, M.D.) (*Abstract 16*, below)

24 October 1960

Myocardial Infarction: Factors in Delayed Recovery. William L. Winters, Jr., M.D.*, Barney Dlin, M.D.*, Samuel B. Hagner, M.D.*, and George W. Russell, M.D.* (Discusser: H. Keith Fischer, M.D.) (*Abstract 17*, below)

Serum Enzymes with Acute Arterial Occlusion of Dog Limbs. Ugo Manzoli, M.D.*, Raymond Penneys, M.D., Samuel Bellet, M.D., and Leonard Feinberg, Ph.D.* (Discusser: Louis A. Soloff, M.D.) (*Abstract 18*, below)

A New Defect in Thyroid Hormone Synthesis. Angelo M. Di George, M.D.* (Discusser: Joseph Rupp, M.D.) (*Abstract 19*, below)

The Effect of Freezing on the Production of Antibody by Bone Marrow. Irwin L. Stoloff, M.D. (Discusser: Rupert E. Billingham, Ph.D.*) (*Abstract 20*, below)

28 November 1960

Pyridoxine Deficiency in Hyperthyroidism. Michael G. Wohl, M. D., Howard A. Levy, M.D.*, Anton Szutka, Ph.D.*, and G. Maldia, M.D.* (Discusser: George E. Farrar, Jr., M.D.) (*Abstract 21*, below)

Therapy of Serious Cardiac Arrhythmias Following Acute Myocardial Infarction. Leonard S. Dreifus, M.D.*, Theodore Oslisk, A.B., and William L. Likoff, M.D. (Discusser: Samuel Bellet, M.D.) (*Abstract 22*, below)

Mode of Action of Quinacrine Inhibition on LE Cell Formation. Neilon Neilson, M.D.*, and John Lansbury, M.D. (Discusser: Harvey F. Watts, M.D.*) (*Abstract 23*, below)

Treatment of Intractable Heart Failure in the Presence of Complete AV Heart Block by the Use of the Internal Cardiac Pacemaker: Report of a Case. Otto F. Muller, M.D.*, and Samuel Bellet, M.D. (Discusser. Thomas M. Durant, M.D.) (*Abstract 24*, below)

23 January 1961

The Use of Disodium EDTA in the Treatment of Obliterative Peripheral Vascular Disease. J. Roderick Kitchell, M.D. (Discusser: Lawrence E. Meltzer, M.D.) (*Abstract 25*, below)

Implication of Nickel as a Pulmonary Carcinogen in Tobacco Smoking. F. William Sunderman, M.D., Ph.D., and F. William Sunderman, Jr., M.D.* (Discusser: Katharine R. Boucot, M.D.) (*Abstract 26*, below)

Biliary Dyskinesia—Discussion of Diagnosis. Franz Goldstein, M.D.* (Discusser: C. Wilmer Wirts, M.D.) (*Abstract 27*, below)

The Neurosurgical Treatment of Spontaneous Intracranial Hemorrhage. Michael Scott, M.D. (Discusser: Nathan S. Schlezinger, M.D.) (*Abstract 28*, below)

SECTION ON MEDICAL HISTORY

16 February 1960

The History of the Tetralogy of Fallot. Helen B. Taussig, M.D., Sc.D.*, Johns Hopkins University School of Medicine.

15 November 1960

Two Landmarks in American Medicine—Their Impact. Truman G. Schnabel, M.D. (*Transactions & Studies*, April 1961).

Rush and Physick—An Important Medical Friendship. George F. Sheldon, A.B.*, University of Kansas School of Medicine (*Transactions & Studies*, July 1961).

Presentation of Edward Bell Krumbhaar Prize III (Medical Student Essay

Contest Award) to Dean Arvan, M.D. (*Transactions & Studies*, January 1961)

SECTION ON OPHTHALMOLOGY[1]

21 January 1960

Devic's Syndrome with an Unusual Etiology—A Clinical-Pathological Case Report. Josefina M. Orteza, M.D.*

Glaucoma Surgery with Silicone Rubber. Richard A. Ellis, M.D.

Carotid Cavernous Sinus Fistula with Some Unusual Ocular Signs. Robert J. Kirschner, M.D.*, and Martin K. Lubrow, M.D.*

18 February 1960

The Trabecular Meshwork by Electron Microscopy. Levon K. Garron, M.D.,* College of Physicians & Surgeons, Columbia University.

17 March 1960

Wegener's Granulomatosis ("Histopathology of Ocular Involvement"). William C. Frayer, M.D.

Bilateral Subconjunctival Granulomatous Lesions. A. E. Wiggs, M.D.*

Flat Retina Preparation in the Study of Diabetic Retinopathy. Robert J. Kirschner, M.D.*

21 April 1960

Complications in Strabismus. Edward A. Dunlap, M.D.*, Cornell University Medical College.

20 October 1960

Nutritional Eye Disease. Don S. McLaren, M.D.*, East African Institute for Medical Research, Tanganyika.

17 November 1960

Concerning the Optic Chiasm, Selected Pathologic Involvements and Clinical Problems. Frank B. Walsh, M.D.*, Johns Hopkins University School of Medicine. (Twenty-third Annual de Schweinitz Lecture.)

15 December 1960

Observations on the Use of a New Cycloplegic-Mydriatic Mydriacyl. Bernard C. Gettes, M.D.

Ataractic and Antiemetic Drugs in Ocular Surgery: A Double Blind Study. J. E. Mishler, M.D.*, and Robison D. Harley, M.D.

The Nevus of Ota, or Oculo-Dermal Melanocytosis ("Ocular Changes"). Thomas H. Cowan, M.D., and Marvin Balistocky, M.D.*

19 January 1961

Neuro-Ophthalmological Implications of the Gerstmann Syndrome: Report of a Case. Robert J. Kirschner, M.D.*

The Ocular Penetration of Declomycin. Dana Newton, M.D.*, Francis P. Furgiuele, M.D.*, and David Seaman, M.D.*

Complications of Photo Coagulation. Edward J. Cannon, M.D.*

9 February 1961

The Management of Ocular Malignancy. Frank W. Newell, M.D.*, University of Chicago School of Medicine.

SECTION ON OTOLARYNGOLOGY[2]

2 February 1960

Symposium on Recent Advances in the Management of Abnormalities of the Paranasal Sinuses: Acute Sinusitis. Herbert P. Harkins, M.D.

Chronic Sinusitis. Austin T. Smith, M.D.

Allergic Sinusitis. Louis E. Silcox, M.D.

Neoplasms of the Paranasal Sinuses Robert D. Harwick, M.D.*

Radiology of the Paranasal Sinuses.

[1] Abstracts of the presentations at the Section customarily appear in the *American Journal of Ophthalmology* and *A.M.A. Archives of Ophthalmology.*

[2] Abstracts of the presentations at this Section customarily appear in the *A.M.A. Archives of Otolaryngology.*

Antolin Raventos, M.D.* (Joint Meeting of the Section on Otolaryngology, College of Physicians of Philadelphia, and the Philadelphia Laryngological Society.)

20 April 1960

Otologic Findings in Menière's Syndrome and Cerebellopontine Angle Tumor. Fred Harbert, M.D. (Discusser: Edmund P. Fowler, Jr., M.D.*)

Angiofibroma of the Nasopharynx. John D. Cunningham, M.D.* (Discusser: James A. Moore, M.D.*)

Sarcoma of the Larynx. Charles M. Norris, M.D. (Discusser: John F. Daly, M. D.*)

Osteomyelitis of the Frontal Bone. William V. Hostelley, M.D.* (Discusser: Orrin E. Anderson, M.D.*)

(Joint Meeting of the Section on Otolaryngology, College of Physicians of Philadelphia, and The New York Academy of Medicine.)

16 November 1960

Tonsillar Malignancy. G. Gordon Snyder, M.D.* (Discussers: John V. Blady, M.D., and Simon Kramer, M.D.*)

Review of the Current Techniques in Tympanoplasty: The use of vein grafts and plastic struts for the improvement of hearing in chronic otitis media and mastoiditis. Woodrow D. Schlosser, M.D. (Discussers: Fred Harbert, M.D., and Douglas Macfarlan, M.D.)

18 January 1961

"Changing Times". Edwin N. Broyles, M.D.*, President, American Laryngological Association.

(Joint Meeting of the Section on Otolaryngology, College of Physicians of Philadelphia, and the Philadelphia Laryngological Society.)

SECTION ON PUBLIC HEALTH, PREVENTIVE AND INDUSTRIAL MEDICINE

18 May 1960

Symposium on Social, Economic and Emotional Factors in Urban Illness. William A. Steiger, M.D., Francis H. Hoffman, M.D., Victor J. LoCicero, M.D.* James F. Rooney, M.S.W.*, and Sheila Scott, R.N., M.S.* (*Transactions & Studies*, January 1961.)

The Hospital as a Community Health Center. Cecil G. Sheps, M.D., M.P.H.*, Graduate School of Public Health, University of Pittsburgh.

Prepayment Plans and the Group Practice of Medicine. Dean A. Clark, M.D.*, Massachusetts General Hospital.

Research in Medical Care. Katharine O. Elsom, M.D., M.P.H.*

Discussion and Summary. Tom F. Whayne, M.D., Dr.P.H.

(Joint Meeting of the Section of Public Health, College of Physicians of Philadelphia, and Pennsylvania Public Health Association, Region One, held at Lankenau Hospital.)

13 December 1960

Presentation of William Harvey Perkins Prize II (Medical Student Essay Contest Award) to Naomi R. Bluestone, B.A. (*Transactions & Studies*, January 1961)

ABSTRACTS

Abstract 1

The Use of Guanethidine (Ismelin) in The Treatment of Hypertension. John G. Kelly, M.D., Edmund L. Housel, M.D., and James W. Daly, M.D.

One of the new agents developed for use in the treatment of hypertension is Guanethidine (2 Octahydro-1 Azocnyl ethyl) guanidine sulfate synthesized by Mull and Associates.

In animal experimentation done by Maxwell, Plummer and their group, the following effects were observed: 1) Intravenous administration of 15 mg./Kg. in neurogenic and renal hypertension dogs was followed by a marked fall in systolic and diastolic pressure, a narrowing of pulse pressure and a marked slowing of cardiac rate. These effects persisted up to one week after a single infusion. 2) Given intravenously it produced marked inhibition of the pressor effects produced by amphetamine and by bilateral carotid occlusion. 3) Following adminis-

tration of the drug, there was no evidence of ganglionic blockade or inhibition of parasympathetic efferent transmission. 4) There was, however, inhibition of response to electrical stimulation of the sympathetic efferents, and 5) pressor response to norepinephrine was exaggerated.

These animal findings suggest that Guanethidine is a potent, long-acting hypotensive agent that produces its effect not by ganglionic blockade, but by blocking transmission at the post-ganglionic sympathetic nerve endings, possibly by inhibiting release of pressor substance or neutralizing it as it is released.

With this knowledge of the drug's action in animals it was our purpose to study the effects of the drug in a group of severe human hypertensives. Fourteen patients were treated, all of whom had long standing hypertension of three to 20 years duration. The average blood pressure prior to therapy was 160/100 or greater, and evidence of cerebral, cardiovascular and/or renal involvement was present in all cases. The first eight patients were hospitalized and serial hematologic, cardiac, hepatic and renal studies were done to guard against toxic effects. The other six patients were selected as representing severe cases doing poorly on current therapy.

While in the hospital, blood pressures were taken four times daily, supine and erect, immediately on standing, and two minutes after standing. In the clinic, blood pressures were taken as above, a physical examination done, and the patients questioned concerning side effects or possible toxic reactions to the drug. The initial dosage of the drug was 25 mg., with drug dosage being adjusted every three to four days in the hospital or at every visit in the clinic.

Results:

In the eight hospitalized cases the onset of hypotensive effects was reached in three to five days. Dosage for effective control varied from 6.25 to 50 mg. daily. In 11 of 14 cases a significant decrease in systolic and diastolic pressure greater than 20 mm. of Hg. was produced in both supine and erect position measurements. All but one patient experienced symptoms of orthostatic hypotension. In one subject the orthostatic effect was so severe, despite dosage adjustment, that the drug had to be discontinued.

The pulse pressure was decreased in all patients, being most marked in the erect position. Bradycardia was noted in 13 instances. In five cases where azotemia was present, the BUN being 30 mg. or greater, a hypotensive effect was achieved with no evidence of worsening of the renal status. When the drug was discontinued, its effects persisted for four to six days. There was no improvement or deterioration in eyeground, renal function or EKG findings during therapy. No evidence of tolerance developed. Side effects included orthostatic hypotension in 13 instances and diarrhea in three cases, controlled by antispasmotics. No evidence of toxicity developed.

Guanethidine appears to be a new approach to the problem of therapy in severe hypertension. Pharmacologically unique in that it acts at the sympathetic endplate, it avoids the unpleasant side effects of ganglionic blockade. It is potent, long-acting, non toxic and has minimal side effects.

Further clinical experience is necessary to clarify its place in therapy, but this drug appears to represent a real improvement over ganglioplegic agents in the treatment of severe hypertension.

Abstract 2

CYCLOPHOSPHAMIDE IN THE MANAGEMENT OF MALIGNANT DISEASE.* Sylvan H. Eisman, M.D., Robert G. Ravdin, M.D., and Peter R. Coggins, III, M.D.

In 1948, Gomori (1) showed that malignant tissue contained increased amounts of the enzyme phosphamidase. It was subsequently demonstrated that it was feasible to synthesize inactive cyclic phosphamide esters of nitrogen mustard, which are then in turn activated by

* Cytoxan (Cyclophosphamide), Mead Johnson & Company brand 2H-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino] tetrahydro-,2-oxide, was generously supplied by Mead Johnson & Company for this study.

phosphamidases (2). In 1957, such a compound, cyclophosphamide, was produced by Arnold and Bourseaux (3). This compound is relatively inert *in vitro*.

This compound has been administered to 95 consecutive patients with inoperable malignant disease. Ten of this group had malignant processes of hematologic origin; the remainder had solid tumors. All patients were followed by objective measurement of tumor masses, measured directly by caliper, or by serial x-ray examinations of lungs, bones, or liver, in the latter category, Thorotrast was used to outline tumor nodules. Only those patients who clearly demonstrated objective reduction in size of tumor nodules were considered to show tumor regression.

Dosage regimens employed were of two classes: I, an initial loading dose of 7.5 mgm./kg./day for 6 days, followed by weekly or biweekly intravenous injections and daily oral therapy aimed to maintain the peripheral white blood count between 1500 and 3000 cells per cu. mm.; II, successive single massive intravenous injections of 45 to 100 mgm./kg. given 18–30 days apart, depending on the white blood cell response.

In either regimen, considerable leukopenia was noted, usually by day 10 to 14 in Regimen I, and somewhat earlier with Regimen II. Toxic side effects noted were nausea, vomiting alopecia, and sterile cystitis. Alopecia occurred in almost all patients, but usually regrowth of hair was noted even while on maintenance therapy. Symptoms of cystitis appeared usually in patients treated by massive doses within 48 hours after injection, and lasted 4 to 5 days.

Clinical response was demonstrated by pain relief in 70% of patients having pain before treatment. Anti-tumor effect was noted in about 33% of those patients considered evaluable at the time of this report. Remission lasted on the average of two months, and when it appeared, it was apparent within 3 to 4 weeks after initiation of therapy. If no response was noted, continued therapy up to 5 months proved to be of not value. When relapse occurred following remission, further treatment was not attended by a second remission.

REFERENCES

1. Gomori, G.: Histochemical Demonstration of Sites of Phosphamidase Activity. Proc. Soc. Exp. Biol. and Med. **69:** 407–409, 1948.
2. Friedman, M., and Seligman, A. M.: Preparation of N-phosphorylated Derivatives of bis-B-chloroethylamine. J. Am. Chem. Soc. **76:** 655–658, 1954.
3. Arnold, H., Bourseaux, F., and Brock, N.: Neuartige Krebs-Chemotherapeutika aus der Gruppe der Zyklischen N-Lost-Phosphamidester. Naturwissenschaften **45:** 64–66, 1958.

Abstract 3

Open Heart Surgery for Mitral Stenosis and Mitral Regurgitation. Henry T. Nichols, M.D., Gumersindo Blanco, M.D., Joseph F. Uricchio, M.D., and William L. Likoff, M.D.

Our approach to the mitral valve by open technique in this series of patients has been the same in all cases. A left posterior lateral thoracotomy approach through the left fifth intercostal space has been used. The uptake catheter to the heart-lung machine has been inserted through a purse-stringed incision in the right ventricular outflow tract and the output catheter has been inserted into the femoral artery. The left atrium has been incised parallel to the atrio-ventricular groove.

In the repair of mitral insufficiency the advantages of the left thoracotomy approach in comparison with the right thoracotomy approach are as follows:

1). Better visualization of the mitral valve.
2). Less danger of air embolization.
3). Single catheter technique avoids superior vena cava blockage.

The advantages of the open technique in comparison with the closed technique in the repair of mitral insufficiency are as follows:

1). Calcium can be removed from the valve.
2). Ruptured chordae can be repaired.
3). Torn or incised leaflets following closed mitral commissurotomy can be repaired.
4). Limited commissurotomy to improve leaflet mobility can be done without fear of increasing the regurgitation.

5). More selective annulus plication can be done and more sutures can be inserted with safety.

A total of 36 consecutive cases of predominant mitral insufficiency have been operated upon in this series. Plication of the mitral annulus in the region of the posterior commissure has been the more common method of repair. In four cases an Ivalon wedge has been inserted to move the mural leaflet away from its annulus toward the septal leaflet. Three cases have required repair of spontaneous rupture of the chordae tendinae. Three cases have required direct leaflet suturing for repair of lacerations produced by previous mitral commissurotomy. There has been a hospital mortality in seven cases for a percentage of 19.4.

The advantages of the open technique in comparison with the closed technique in the performance of mitral commissurotomy are as follows:

1). Calcium can be removed from the valve.
2). Clots can be removed from the atrium.
3). Production of significant mitral insufficiency can be avoided.
4). Subvalvular fusion can be more adequately and safely relieved.
5). Any associated mitral insufficiency can be repaired.

A total of twenty consecutive cases of mitral stenosis have been operated upon in this series. Four patients have had previous closed mitral commissurotomies. Calcium was removed from the valve in five cases. Marked subvalvular fusion was relieved in seven cases. Atrial clots were removed in six cases. No significant regurgitation was produced in any of these patients. There were three hospital deaths for a percentage of 15.

Abstract 4

THE HEART IN GLYCOGEN STORAGE DISEASE. Otto F. Muller, M.D., and Samuel Bellet, M.D.

Diseases of glycogen storage are relatively rare disorders which are due to congenital and familial disturbance in carbohydrate metabolism. Glycogen may accumulate in practically every organ. A recent attempt to classify the various resulting disorders led to the division into four different types (Cori, Andersen, Recant). These types are specific disease entities with the same expression of abnormality, the deposition of glycogen; but pathogenesis, clinical and pathological findings are strikingly different.

The clinical, pathological and biochemical findings and abnormalities of each type were presented. The heart is involved in two types. There is extensive cardiac involvement in the type which presents generalized glycogenosis in all organs which normally contain glycogen (Type 2). The glycogen has a normal molecular structure, and any enzyme deficiencies could not be detected thus far. Type 3 also shows cardiac storage; the glycogen structure is abnormal approaching limit dextrin. The debrancher enzyme (amylo-1,6-glucosidase) is absent in skeletal and heart muscle.

Clinical and postmortem findings of an eight months old infant with generalized glycogen storage (Type 2) were presented. Glycogen accumulation was seen in the myocardium, skeletal muscle, smooth muscle, liver, kidney, central nervous system and autonomic ganglia. Storage in the ganglia of the plexus myentericus (Auerbach), which gave rise clinically to Hirschsprung's disease, could explain the feeding problems and constipation observed in this and other cases mentioned in the literature. The infant died of cardiac failure due to replacement of the myocardial fibers by excessive amounts of glycogen. This condition is probably more common than review of the literature would indicate; it is therefore often missed during routine clinical and necropsy studies.

Abstract 5

ALVEOLAR HYPOVENTILATION DUE TO INVOLVEMENT OF THE RESPIRATORY CENTER BY OBSCURE DISEASES OF THE CENTRAL NERVOUS SYSTEM. Theodore Rodman, M.D.

Until recently alveolar hypoventilation had been recognized only as a rather obvious complication of such diseases as pulmonary emphysema, poliomyelitis, and following the administration of large doses of central nervous system depressants. Recently, hypoventilation

has been recognized as an unusual complication of extreme obesity. Even more recently a few isolated cases have been described with alveolar hypoventilation in the absence of obvious underlying disease. In these cases, disease of the medullary respiratory center has been inferred.

TABLE 1

CLINICAL FEATURES OF THE PRIMARY HYPOVENTILATION SYNDROME

1. Little or no dyspnea in the presence of cardiac enlargement.
2. Chief Complaint: Easy fatigability, somnolence, headache.
3. Cyanosis and intermittent respirations particularly during sleep.
4. Polycythemia without leukocytosis, thrombocytosis, or splenomegaly.
5. EKG: Vertical electrical axis progressing to right ventricular hypertrophy and strain.
6. X-Ray: Cardiac enlargement primarily right ventricular with prominence of the pulmonary artery—No evidence of primary lung disease.
7. Increased arterial plasma CO_2 content.

TABLE 2

PULMONARY FUNCTION STUDIES IN THE PRIMARY HYPOVENTILATION SYNDROME

1. Little or no evidence of lung disease.
2. Alveolar hypoventilation.
3. Arterial blood gas changes of chronic respiratory acidosis.
4. Return toward normal of arterial blood gases on voluntary hyperventilation.
5. Abnormal ventilatory response to chemical respiratory stimulants. ($\uparrow CO_2$, $\downarrow O_2$)

During the past three years we have studied four patients who are examples of this "Primary Hypoventilation Syndrome". Our experience suggests that this disease is more common than is indicated by the presence of a half dozen cases in the world literature (1–6), and that the diagnosis may be missed because the clinical picture resembles other diseases.

The first patient was a 41 year old schizophrenic man in whom congenital heart disease was suspected because of cyanosis, polycythemia, and right ventricular enlargement by x-ray and electrocardiogram. Cardiopulmonary function studies, however, showed no evidence of primary heart or lung disease but demonstrated a profound derangement of the respiratory center with almost complete loss of sensitivity to CO_2 stimulation.

The second patient was followed for two years with a diagnosis of polycythemia vera until cardiac enlargement and electrocardiographic changes suggestive of cor pulmonale developed. Studies of cardiopulmonary function again demonstrated absence of respiratory center sensitivity to CO_2.

A diagnosis of congestive heart failure secondary to arteriosclerotic heart disease had been made in the third patient. Studies of pulmonary function were requested because of cyanosis and polycythemia. They demon-

THE PATHOPHYSIOLOGY OF THE PRIMARY HYPOVENTILATION SYNDROME

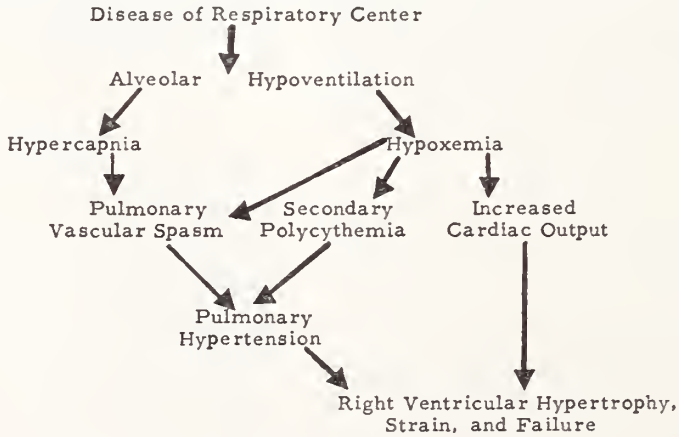


FIG. 1

strated deranged respiratory regulation with only slight reduction in sensitivity to CO_2 but a paradoxical response to hypoxemia.

Narcolepsy was the provisional diagnosis made in the fourth patient, a 27 year old man with cervical cord syringomyelia. Because he was observed to have periods of apnea, studies of respiratory center function were done and demonstrated a marked reduction in sensitivity to CO_2 stimulation.

It is suggested that, at least in fully developed cases, the diagnosis can be suspected on clinical grounds (Table 1) and appropriate studies of pulmonary function (Table 2) done to establish the diagnosis.

Etiologic diagnosis and the description of morphologic changes in the central nervous system must await post mortem study, but the evidence for involvement of the respiratory center is quite convincing.

The clinical picture is readily understood on the basis of the demonstrated derangement of cardiopulmonary dynamics (Figure 1).

REFERENCES

1. Ratto, O., Briscoe, W. A., Morton, J. M., and Comroe, J. H., Jr.: Anoxemia secondary to polycythemia and polycythemia secondary to anoxemia. Am. J. Med. **19:** 958–965, 1955.
2. Pare, P., and Lowenstein, L.: Polycythemia associated with disturbed function of the respiratory center. Blood **11:** 1077–1084, 1956.
3. Medical Grand Rounds, Massachusetts General Hospital. Hypoventilation syndrome. Edited by Smith, L. H., Am. Prac. & Digest Treat. **7:** 1165–1172, 1956.
4. Richter, T., West, J. R., and Fishman, A. P.: The syndrome oi alveolar hypoventilation and diminished sensitivity of the respiratory center. New England J. Med. **256:** 1165–1170, 1957.
5. Rodman, T., and Close, H. P.: The primary hypoventilation syndrome. Am. J. Med. **26:** 808–817, 1959.
6. Hadorn, Von W., und Scherrer, M.: Essentielle alveoläre Hypoventilation mit cor pulmonale. Sonderabdruck aus der Schweizerischen Medizinischen Wochenschrift 89. Jahrgang 1959, Nr. 25, Seite 647.

Abstract 6

Postgastrectomy Steatorrhea—Its Relationship to Afferent Limb Stasis and Bacterial Flora. Franz Goldstein, M.D., C. Wilmer Wirts, M.D., and Simon Kramer, M.D.

Impaired absorption of fat has been noted in about 50 per cent of patients subjected to a Billroth II type of subtotal gastric resection for benign peptic ulcer. The steatorrhea is occasionally of a severe degree and is among the causes of malnutrition so frequently encountered in postgastrectomy patients. Although there is an increasing awareness of the frequency of this type of malabsorption, there is no agreement as to its cause.

Inadequate stimulation of pancreatic juice and bile secretion, poor mixing of food with digestive secretions, and increased motor activity of the small bowel have in the past been held largely responsible for the production of post, gastrectomy steatorrhea. However, treatment based on these concepts has proven ineffective in increasing absorption sufficiently to improve the nutritional status of affected patients.

The authors (1, 2) have previously suggested that the mechanism of postgastrectomy steatorrhea is similar to that which causes malabsorption in patients with blind loops or diverticulosis of the small bowel, and that it is related to stasis and bacterial growth in the afferent limb of the gastroenterostomy. An analogy between postgastrectomy steatorrhea and the blind loop syndrome had been postulated earlier by British investigators (3, 4).

Ten unoperated control patients and 23 patients with Billroth II subtotal gastrectomies 15 without and 8 with steatorrhea, have been studied. Duodenal fluid in the control patients and afferent loop fluid in the postgastrectomy patient was secured by intubation and was subjected to quantitative bacterial cultures. Fat absorption was estimated by microscopic stool examinations, I-131 labeled triolein fecal excretion studies, and more recently also by fat balance measurements.

Bacterial counts in the unoperated control patients showed a mean of 18,940 colonies per cc. The mean of the bacterial counts in the steatorrhea-free postgastrectomy group was 602,740 colonies per cc. The two patients with most severe, disabling steatorrhea had bacterial counts of 250,000,000 and 750,000,000

colonies per cc., respectively. In all steatorrhea patients, the predominating organism was a Gram-negative bacillus, the flora generally resembling colonic flora in both quantity and quality.

In the two most severely affected patients, specific antibiotic therapy based on sensitivity determinations of recovered organisms resulted in striking improvement in weight and fat absorption which coincided with a return of the afferent limb flora to normal.

Analysis of clinical data revealed that postgastrectomy steatorrhea occurred in patients with anacidity and with long, often antiperistaltic, poorly emptying afferent limbs where prolonged stasis permits the establishment of a resident bacterial flora. An analogy between postgastrectomy steatorrhea and the blind loop syndrome has been demonstrated.

REFERENCES

1. Wirts, C. W., Goldstein, F., Calaresu, F. R., Kramer, S., and Concannon, J.: The Mechanism of Absorption of Radioactive Fat. Proceedings of the World Congress of Gastroenterology, Washington, D. C., 1958, Williams and Wilkins Co., vol. 1, p. 451.
2. Wirts, C. W., Goldstein, F., and Wise, R. I.: Postgastrectomy Steatorrhea—A Variant of the Blind Loop Syndrome. Am. J. Gastroenterol. **31:** 250, 1959.
3. Butler, T. J., Capper, W. M., and Naish, J. M.: Ileo-Jejunal Insufficiency Following Different Types of Gastrectomy. Gastroenterologia **81:** 104, 1954.
4. Naish, J. M., and Capper, W. M.: Intestinal Cul-de-Sac Phenomena in Man. Lancet **2:** 597, 1953.

Abstract 7

Pneumatosis Cystoides Intestinalis: Report of Two Cases. Lucy J. Balian, M.D., Allen J. Steinberg, M.D., and Burton Schaffer, M.D.

Two clinically similar cases of pneumatosis cystoides intestinalis, a disease which is characterized by multiple, gas-filled cysts within the intestinal wall, are reported in detail. Both cases, one, an infant, and the other, an adult, were autopsied at the Philadelphia General Hospital within the same week. Approximately two hundred and fifty human cases have been reported in the literature, although the disease is known to occur commonly in hogs. It was first described in swine by a Russian author in 1730, whereas the first human case was not reported until 1754.

The disease generally occurs in one of two forms. In adults, it is usually benign and is characterized by the presence of subserosal cysts of sizes ranging from a few millimeters to several centimeters in diameter. Over fifty per cent of the cases are found to occur in patients with some form of pyloric ulcer or pyloric obstruction. The cysts may resolve spontaneously, rupture and produce a pneumoperitoneum, or they may become large enough to cause intestinal obstruction. The disease is more serious in infants, since it is most commonly associated with a form of enterocolitis, gastro-intestinal hemorrhage, or perforation of the bowel wall. In these cases, the cysts are localized within the submucosa and the wall of the bowel appears to be emphysematous.

The cysts are thought to be dilated lymphatics. However, there is no agreement as to their pathogenesis. Most students of the entity support the mechanical theory, which assumes that the gas is forced through a fissure in the intestinal mucous membrane or enters the lymphatics and spreads along the mesentery. Other less likely explanations include dietary deficiency factors, or gas production by bacterial action.

Abstract 8

Studies on Pulmonary Osteoarthropathy. H. Edward Holling, M.D., Robert S. Brodey, D.V.M., and H. Christine Boland, B.S.

Secondary hypertrophic osteoarthropathy is a chronic inflammation of connective tissue, periosteum and joints sometimes associated with pulmonary neoplasm in man and in dogs. Greatly increased blood flow occurs in the affected tissues and since this develops with the condition and diminishes with relieving procedures, we have used it to indicate changes occurring in acute experiments.

Possible mechanisms of the condition which have been considered are:

(a) Humoral. Cross circulation experiments

between a normal dog and one with osteoarthropathy failed to show any transfer of a causative humoral substance.

(b) Opening of arteriovenous communications. The oxygen tensions of arterial blood in human and canine patients when breathing air and breathing oxygen failed to show evidence of abnormal pulmonary venoarterial shunt.

(c) Reflex. This mechanism seemed the most likely since it has been shown that vagotomy on the side of a unilateral lung lesion may cause prompt regression of signs and symptoms. In dogs with bilateral neoplasm, we have found that a unilateral vagotomy may be without effect though a bilateral vagotomy promptly reduces the hyperemia. This is attributed to interruption of afferent rather than efferent impulses for atropinization of the animal is without this effect. Such afferent impulses appear to arise from the thoracic cage in some cases, from the lungs in others.

In normal subjects, reduction of intrathoracic blood volume by means of pressure breathing reflexly causes a reduction of limb blood flow. This does not appear to be the reflex involved in osteoarthropathy because pressure breathing is without effect, moreover, the increased blood flow appears to be in connective tissue rather than in vessels of the muscles.

The hyperemia is probably mediated by vasodilator fibers for it is more intense than that which follows denervation. However, it does not appear to travel in the lumbar sympathetic outflow for lumbar sympathectomy and the sympathetic blocking agent, bretylium, do not affect the hyperemia.

Abstract 9

Comparative Bioassay of Diuretics. Morton Fuchs, M.D., and John H. Moyer, M.D.

The comparative bioassay of diuretics in patients with edema presents great difficulty. In the edematous patient there are multiple factors influencing sodium and water transfer at the renal tubular level. The evaluation of the pharmacologic characteristic of a drug in the edematous patient must be done through the distortion produced by the disrupted homeostatic mechanisms in this patient. A patient with refractory edema may show no response to any of the potent diuretics and there would be no medium for measuring comparative effectiveness of drugs.

Average weight loss in heart failure patients that will respond to diuretic agents may be used as a measure of comparative diuretic efficacy. However, the availability of the same patients for checking the different drugs and the changing physiology of the individual paients makes this a crude form of bioassay.

Another method of comparing effectiveness of diuretics is to measure their effects on sodium excretion under controlled metabolic conditions of sodium and fluid balances. This can be done in persons whose cardiovascular and renal physiology is normal and no edema is present. With these controlled circumstances, control sodium excretions are determined and the quantity of sodium excreted above control levels due to a given drug can be measured. The average increase in sodium excretion of a group of patients given one drug is then compared to the increased sodium excreted by another group of patients given another drug. With this method of bioassay there is difficulty in using the same patients for the different drugs and variations in sodium excretion in individual patients is great enough to obscure differences in sodium excreting effects between drugs.

Another technique for comparing the effects of two drugs on sodium excretion is presented.

The control rate of sodium excretion per minute in a patient with no edema or abnormal sodium retaining influences on the kidney is determined. A greater than maximum effective dose of a drug is given intravenously and the rate of sodium excretion per minute is determined every half hour until a plateau or constant increased rate above control levels is obtained. The next drug in comparative dosage is then given intravenously and further evaluation of rate of sodium excretion is determined. If the second drug has greater effects on sodium excretion than the first there will be a further rise in the rate of sodium excretion per minute. If it does not there will be no change. This pro-

cedure can then be repeated in the same patient after a day or two of sodium repletion. The order of administration of the drugs is reversed to check the reliability of the original experiment. This method can also be applied for potassium excretion as well as other electrolytes This latter method for comparative effectiveness of diuretics by human bioassay may have promise. However, it must be remembered we are again comparing drugs in individuals for whom the drug was not created and therefore we are again speculatively projecting the pharmacologic effects of these drugs on the normal patient into the pathologic edematous patient.

Abstract 10

EFFECTS OF FAT UPON CORONARY AND PULMONARY CIRCULATIONS: AN EXPERIMENTAL STUDY.* Peter T. Kuo, M.D., Arthur F. Whereat, M.D., Arthur A. Altman, M.D., and James W. West, Ph.D.

A number of investigators have observed, although somewhat inconstantly, certain undesirable effects of lipemia in humans. These include: an increase in the coagulability (1) and viscosity of the blood (2), sludging of the red cells (3), and agglutination and adhesiveness of the blood elements (4). Clinically, we and others (5–7) have found that acute hyperlipemia may act in some way to aggravate the symptoms and signs of arterial insufficiency in patients with severe coronary and peripheral vascular diseases. And, subjective and objective evidences of improvement in tissue oxygenation were demonstrated in patients with idiopathic hyperlipemia and atherosclerosis, following the clearing of their lipemias (8, 9).

In this study, we hope to learn the mechanisms involved in the interference of tissue oxygen by a high concentration of chylomicrons in the blood stream.

Myocardial scars were produced in dogs by ligating one or more branches of the anterior descending coronary artery. Twenty dogs which have survived the operation for 4–12 weeks, and thirteen animals with intact coronary circulation were used for the study. Coronary blood flow was measured by the nitrous oxide method of Eckenhoff and Goodale and their associates. Cardiac output was estimated by the Fick principle. A standard limb electrocardiogram, femoral arterial pressure, and at intervals, the pulmonary arterial pressure were recorded simultaneously with a multichannel oscillograph. Blood samples taken from the coronary sinus, pulmonary and femoral arteries were analyzed for oxygen and carbon dioxide contents.

In each animal, immediately after the completion of the control set of observations, a commercial fat emulsion (10% sesame oil in glucose and water and an emulsifying agent) or 10–15% lipemic plasma (obtained from a donor dog) was given by intravenous infusion at the rate of 50–60 drops per minute. The second set of physiologic measurements was made in the same animal within 25–35 minutes of the completion of the control run. To estimate the degree of lipemia produced, blood sample was taken at the end of each coronary flow run from the same animal for total esterified fatty acid determinations.

Infusion of a commercial fat emulsion to ten normal animals, and lipemic plasma to three dogs in the same group produced identical results. During the control period, the mean coronary blood flow of these animals was 96 ml./100 gm. left ventricle/min. with a mean oxygen extraction of 11.10 vol. % and a myocardial oxygen consumption of 10.3 ml./100 gm. left ventricle/min. Fat infusion decreased their mean coronary blood flow to 82 ml./100 gm. left ventricle/min. However, the mean myocardial A-V difference remained relatively unchanged at 11.0 vol. %. This resulted in a significant decrease on myocardial oxygen consumption to a mean of 8.9 ml./100 gm. left

*From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania and Department of Pharmacology and Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

This work was done during the tenure of an Established Investigatorship of the American Heart Association.

The study is supported in part by grants from The Life Insurance Medical Research Fund and the American Heart Association.

ventricle/min. Fat infusion given at this rate produced no significant changes in the mean arterial pressure of these animals while their coronary and total peripheral vascular resistances were slightly increased.

All animals became hyperpneic with the infusion. Their blood gas studies showed a simultaneous fall in the arterial carbon dioxide and oxygen contents. Their mean arterial oxygen saturation decreased 2.5% and their carbon dioxide content was lowered by 5.4 vol. %. No significant change in the pulmonary arterial pressures was observed with these changes in blood gases.

Induction of lipemia in dogs with myocardial scars appeared to have caused a slightly more marked reduction in the mean coronary blood flow (a mean drop of 16.5 ml. vs. 14 ml. in the control group) and in myocardial oxygen consumption (a mean decrease of 1.7 ml. vs. 1.4 ml. in normal dogs) than animals in the control group. However, the differences between the two groups were found to be of no statistical significance. The mean arterial oxygen saturation of dogs with myocardial scars dropped 2.8% and their mean arterial carbon dioxide content dropped 4.7% with the fat infusion.

Respiratory quotient of the heart, and the total body oxygen consumption of the animals, and their hematocrit were not significantly altered following fat infusion. No change in the coronary circulation and arterial blood gases was observed in dogs which received the fat-free emulsion base infusions.

The study indicates that acute lipemia can exert certain measurable effects upon the pulmonary and coronary circulations in dogs with and without myocardial scars. The changes observed here are somewhat similar to: (1) those observed by Bing and his associates in experimental coronary arterial embolization (10), and (2) those obtained by Niden and Aviado in experimental pulmonary embolization (11), but of a much milder degree. The chylomicrons may impose a limitation to myocardial oxidation through a combination of these and other mechanisms.

REFERENCES

1. Duncan, G. G., and Waldron, J. M.: The Effects of Ingested Fat on Blood Coagulation. Tr. Am. Assoc. Physicians **179:** 62, 1949.
2. Swank, R. L.: Effect of High Fat Feedings on Viscosity of the Blood. Science **120:** 3115, 1954.
3. Knisely, M. H., Bloch, E. H., Eliot, T. S., and Warner, L.: Sludged Blood. Science **106:** 431, 1947.
4. Cullen, C. F., and Swank, R. L.: Intravascular Aggregation and Adhesiveness of Blood Elements Associated with Alimentary Lipemia and Injections of Large Molecular Substances. Effect on Blood-brain Barrier. Circulation **9:** 335, 1954.
5. Kuo, P. T., and Joyner, C. R., Jr.: Pectoris Induced by Fat Ingestion in Patients with Coronary Disease. J.A.M.A. **158:** 1008, 1955.
6. William, A. V., Higginbotham, A. C., and Knisely, M. A.: Increased Blood Cell Agglutination After Ingestion of Fat, a Factor Contributing to Cardiac Ischemia, Coronary Insufficiency and Anginal Pain. Angiology **8:** 29, 1957.
7. Fulli, V., and Rossi, B.: Plasma Turbidity Changes and Electrocardiographic Alterations Induced by Alimentary Hyperlipemia in Anginal Patients Before and After the Administration of Gastricmucin. Circulation **18:** 400, 1958.
8. Martt, J. M., and Connor, W. E.: Idiopathic Hyperlipemia Associated with Coronary Atherosclerosis. Arch. Int. Med. **97:** 492, 1956.
9. Kuo, P. T., Whereat, A. F., and Horwitz, O.: The Effect of Lipemia Upon Coronary and Peripheral Arterial Circulation in Patients with Essential Hyperlipemia. Am. J. Med. **26:** 68, 1959.
10. Bing, R. J., Castellanos, A., Gradel, E., Lupton, C., and Siegal, A.: Experimental Myocardial Infarction: Circulatory, Biochemical and Pathological Changes. Am. J. Med. Sci. **232:** 533, 1956.
11. Niden, A. H., and Aviado, D. M.: Effects of Pulmonary Embolism on the Pulmonary Circulation with Special Reference to Arteriovenous Shunts in the Lung. Cir. Research **4:** 67, 1956.

Abstract 11

Experiences with Inhibitors to the Plasminogen-Plasmin System in Man.* George

* From the Division of Cardiology, Philadelphia General Hospital. This work was supported by a grant from the Southeastern Heart Association of Pennsylvania, and was done with the technical assistance of Jean Schraeder.

Tsitouris, M.D., Herschel Sandberg, M.D., and Samuel Bellet, M.D.

In the human organism there is an equilibrium between factors tending to produce thrombi and those tending to dissolve them (1). The fibrinolytic system consists of an inactive precursor, plasminogen, which under the influence of activators of tissue, blood, urine or bacterial origin, is capable of being converted into the active proteolytic and fibrinolytic enzyme plasmin (2). There are also substances which inhibit plasmin and the activation of plasminogen to plasmin.

Our interest in these inhibitors arose while we were utilizing an experimental lot of human fibrinolysin to treat a patient with status anginosus. His plasma, both during and after the infusion of the enzyme, was unable to lyse a standard fibrin clot. Dilutions of the same lot of fibrinolysin in imidazole-saline buffer, however, dissolved the clot readily. This observation led us to suspect that increased amounts of anti-thrombolytic substances might be present in the plasma during thrombo-embolic disease states. Methods were devised to investigate this problem.

The subjects of this study consisted of 3 groups: (1) Twenty-nine members of the resident and laboratory staff of Philadelphia General Hospital (control group). (2) Fifty-eight patients with acute myocardial infarction. Twenty-one of these received no heparin; the remainder had been anticoagulated with heparin. (3) Twenty-two subjects with other thrombo-embolic disorders.

The following studies were performed: (1) Plasma fibrinogen concentration. (2) Anti-thrombolysin lysis times. An incubation mixture was employed consisting of (1) 0.2 ml of 1% fibrinogen in imidazole-saline buffer; (2) 0.2 ml of human thrombin in ISB; (3) 0.2 ml of the plasma to be tested; (4) 0.4 ml of Thrombolysin in ISB. The Thrombolysin dilutions consisted of 80, 40, and 20 Merck units respectively. The times required to lyse the clot formed by this mixture was considered to be a measure of the inhibitory activity to the plasmin-plasminogen system of the test plasma.

In the control group the mean anti-Thrombolysin lysis time against 80 Merck units of Thrombolysin was 211 ± 47 seconds; against 40 units 468 ± 146 seconds; against 20 units 755 ± 101 seconds. The mean plasma fibrinogen concentration was 305 ± 25 mg./100 ml.

Both groups of patients with acute myocardial infarction were found to have considerably longer anti-Thrombolysin lysis times than were found in the control group. There was no significant difference between those who had been anticoagulated with heparin and those who had received no heparin. The patients with other thrombo-embolic disorders also showed increased inhibitor activity.

The plasma fibrinogen concentrations of the thrombo-embolic and myocardial infarction groups were also considerably higher than those of the control group.

When increased concentrations of fibrinogen were added to normal plasma, however, concentrations of fibrinogen well above 1000 mg. per cent had to be employed before similar elevations of anti-Thrombolysin lysis times could be obtained.

Following the administration of large doses of Thrombolysin to patients with thrombo-embolic disease, the anti-Thrombolysin lysis times were markedly diminished, the plasma fibrinogen decreased to a much lesser degree.

It was felt that these inhibitors were probably identical with the Trypsin inhibitors described by Shulman (3) and the α_1 and α_2 plasmin inhibitors of Norman (4).

REFERENCES

1. Astrup, T.: Role of Blood Coagulation and Fibrinolysis in the Pathogenesis of Arteriosclerosis. Connective Tissue, Thrombosis, and Atherosclerosis. Irving Page, Editor, N. Y., Academic Press Inc., 1959.
2. Astrup, T.: Fibrinolysis in the Organism. Blood **11:** 781, 1956.
3. Shulman, N. R.: Demonstration that separate proteolytic inhibitors exist in serum; their distinctive properties and the specificity of their action. J. Exper. Med. **95:** 593, 1952.
4. Norman, P. S., and Hill, B. M.: Physical properties of the two plasmin inhibitors in plasma. J. Exper. Med. **108:** 639, 1958.

Abstract 12

CHRONIC CHOLECYSTITIS: INDICATIONS FOR REVISION OF THE CLINICAL DIAGNOSIS. Edwin L. Lame, M.D.

For several years, patients coming to the Presbyterian Hospital of Philadelphia for cholecystograms have been given a special examination by the author, comprising a history-interview, abdominal palpation, fluoroscopy of the chest and abdomen, erect fluoroscopic spot-films of the gall bladder, and the usual film study. Intravenous, repeat and other special study methods have been used when needed. This experience has revealed marked discrepancies and unreliability in the classical basis of a clinical diagnosis and has indicated a need for analysis of clinical signs and a close study of roentgen methods. Such a review has been effected by the detailed examination of 200 patients coming from cholecystograms (100 "normals" and 100 rigidly confirmed cholecystitis patients).

The abnormal cholecystogram has been used as the first indication of cholecystitis, but only those having unquestioned gall stones or a pathologic diagnosis of cholecystitis have been placed in the abnormal group. These are regarded as absolutely confirmed.

The normal group includes only those who showed completely normal opaque contrast studies, as determined by a roentgen technic especially designed to demonstrate stones and regarded as most accurate. Patients disclosing even slight reduction of opaque material in the gall bladder (without stones) were not admitted to the normal group.

Symptoms

A list of 23 symptoms was presented to each patient for answer, after each had an opportunity to volunteer her own complaints. The interrogator did not know the roentgen diagnosis at this time.

Of the first 5 in the abnormal group, 4 are duplicated in the first 5 of the normals.

The right upper quadrant pain stands out as a really valuable symptom, occurring in each of 5 analyses much more often in the cholecystitis group. Furthermore, it is less prone to occur in non-biliary disease than any other symptom. This study has established right upper quadrant pain as the outstanding symptom in chronic cholecystitis.

Cholecystitis	*Order of Incidence*	*Normal Gall Bladder*
Gas	1	Indigestion
Belching	2	Gas
Indigestion	3	Belching
Nausea	4	More comfort A.C.
R.U.Q. pain	5	Nausea

The classical symptoms of cholecystitis occurring about equally or more in the *normal* gall bladder patients as compared to the abnormal are: indigestion, epigastric pain, heartburn, heaviness, dizziness and back pain, with gas and belching only slightly more in the cholecystitis group. This finding relegates many of the old favorites to the category of general and non-specific digestive tract symptoms, occurring in many ailments and creating large and numerous overlaps. Recent observations by other students in this field corroborate this sort of data.

Symptom occurrence which is markedly greater in cholecystitis than in normal patients (in order of difference) is as follows:

1. Poor appetite ..... 29 — 2
2. R.U.Q. pain ..... 45 — 10
3. Weight loss ..... 27 — 11
4. Vomiting ..... 30 — 13
5. Nausea ..... 45 — 22
6. Constipation ..... 30 — 18

(Weight loss and constipation may be considered interlopers here and others might have excluded them. They were included for completeness because many patients volunteered them, not because they are considered valuable.)

Nausea loses some of its diagnostic value in being #5 of the complaints in normals. This leaves anorexia, right upper quadrant pain, vomiting, and, perhaps, nausea as the only valuable symptoms. These are notably similar to the statistics for the first 100 abnormals

analyzed (a group less rigidly selected, but comprising 66% of the final abnormal group):

100 Abnormals Analyzed	*More Rigidly Selected Abnormals*
1. Epigastric pain	1. Anorexia
2. R.U.Q. pain	2. R.U.Q. pain
3. Vomiting	3. Vomiting
	4. Nausea

Finally, the ratio of symptoms *per patient* in the abnormal and normal classes is revealing. This material was studied progressively as the numbers grew. The comparisons are as follows:

Symptoms	
Cholecystitis/Normal Gall Bladder	*Ratio*
4.8/3.9	1.23
4.75/3.5	1.36
4.9/3.5 final group	1.40

In summary, many of the so-called classical symptoms of cholecystitis apparently belong to several digestive disturbances; the ratio of complaints offered by the cholecystitis patient to the normal biliary patient is less than 1.5; some symptoms—anorexia, right upper quadrant pain, vomiting and nausea—stand out as useful diagnostic signs, the most valuable being right upper quadrant pain.

Food Intolerance

The food history was secured by asking the patient to state tolerance with comfort or intolerance to each separate food of a group of 17. "Fried foods" and "fats" were used as samples, but they were the only collective terms applied and 15 other food types were used in this testing. It has been noted repeatedly that these 2 terms ("fried food" and "fats") may be the only ones used in securing a food history and that answers by the patient are correspondingly unreliable. The inference is strong that public sentiment and propaganda are important opinion makers. By requesting separate answers for each type of food memory and independent thought were stimulated and, perhaps, a more valid history was produced.

Of the first 6 intolerable foods, 5 are common to both groups:

Abnormal Gall Bladder	*Order of Intolerance*	*Normal Gall Bladder*
Fats	1	Cabbage
Cabbage	2	Fats
Nuts	3	Fried foods
Pork	4	Pork
Fried foods	5	Spices
Bacon	6	Bacon

In the original 100 abnormals analyzed (criteria less rigid than later), the first 7 and the first 11 intolerables are the same as in the final 100 abnormals. This is a reassuring consistency.

In the final analysis between normals and abnormals, only 1 of the first 7 intolerables in the normal group failed of being in the first 7 of the cholecystitis group; and the first 10 intolerables of each group were the same.

Milk products and egg were consistently at the lower end in both groups and failed to yield any worthwhile differential.

Those foods intolerable to as many or more patients without cholecystitis than with cholecystitis were: apple, butter, cheese, ice cream, egg, milk, spice.

The foods revealing the largest differences and being greater offenders to the cholecystitis patients were: fats 73% (normals 56%), nuts 59% (normals 41%), oils 49% (normals 36%). Such differences may aid diagnosis in a large series, but are of doubtful value for the individual patient.

Reviewing all the data on foods, it is highly questionable that any reliable diagnostic aid can be had in a food history; and it is obvious that many of the old demons do not confine their bad repute to biliary patients.

Conclusions

Personal experience in interviewing patients coming for cholecystograms has demonstrated a great degree of confusion and variability in the clinical history obtained and has shown wide discrepancies between the clinical and the roentgen basis of diagnosis. This has occurred in a period when the roentgen method has reached a high degree of accuracy. A statistical

analysis was undertaken to illuminate the ill-defined clinical criteria.

An analysis of symptoms indicates that many of the classical ones occur in non-biliary patients and probably belong to several disgestive disturbances; that anorexia, right upper quadrant pain, vomiting and nausea appear to be useful diagnostic aids, the most reliable being right upper quadrant pain.

The study of foods shows a history of intolerance in biliary and non-biliary patients that is quite general and impressively non-diagnostic. The differential values of fats, nuts and oils are the best, but probably too small for reliability in individual diagnosis.

Abstract 13

Delirium Tremens: An Analysis of Fatalities Occurring at the Philadelphia General Hospital in a Nine-Year Period. Morton E. Tavel, M.D., Warren Davidson, M.D., and Thomas D. Batterton, M.D.

Although in recent years the mortality rate associated with delirium tremens has been greatly reduced, this disease still remains a management problem. Recent investigation has revealed that delirium tremens results from rapidly falling blood alcohol levels in patients who are chronically addicted to alcohol. Such information places delirium tremens in the category of a drug withdrawal syndrome and should aid in planning rational therapy.

During the years 1950 to 1958 inclusive, thirty-nine of 330 admissions to the Philadelphia General Hospital succumbed to delirium tremens, creating a mortality rate of 11.8%. Careful analysis of fatal cases showed that the group of admissions suffered a wide variety of serious complications, most common of which were pneumonia and liver disease (fatty metamorphosis and cirrhosis). Only eighteen deaths appeared to be attributable directly to the delirium tremens. The patients composing this latter group usually developed hyperthermia (temperature of 104° or greater); convulsive seizures were common, also. Fever reached its maximum intensity on the day of death, a period which usually occurred three to four days after the onset of withdrawal symptoms. Death generally followed a period of coma and shock. Central nervous system dysfunction probably accounts for the fever although dehydration undoubtedly contributes to the process. In order to salvage patients with such symptoms, careful replacement of the tremendous fluid and electrolyte losses is necessary. This fact was corroborated during study of the survivors manifesting hyperthermia.

Diligence in discovering and treating intercurrent illness and good supportive care remain staples of good therapy. Chemical and hormonal agents are at times useful adjuncts. Paraldehyde and barbiturates still remain highly desirable for sedation (despite the recent advent of tranquilizers) since they probably substitute for the effect of alcohol on the central nervous system, thereby ameliorating withdrawal symptoms. Hydrocortisone given intravenously appears to be useful for hyperthermic patients or for those manifesting vascular collapse. Parenteral magnesium may prove useful in therapy, particularly for patients manifesting convulsive seizures and hypertonicity. It is the authors' opinion that these patients are best managed on a medical or metabolic ward under the close supervision of an internist.

Abstract 14

Identification of Urate Crystals in Gouty Synovial Fluid. Daniel J. McCarty, M.D., and Joseph L. Hollander, M.D.

Aspirated fluid from gouty joints has been found in the past to contain crystals of urate, but it was thought that this finding was of such inconstancy as to rarely be of clinical aid in the differential diagnosis of joint disease. Our experience to date indicates that the fluid from 23 of 32 patients contained the typical rod-shaped crystals by ordinary light microscopy. All 7 who had tophaceous gout showed

abundant urate crystals. Of the 22 with nontophaceous gout, 16 showed typical crystals in the fluid. In 4 of the 9 patients who showed no crystals, the diagnosis of gout still has not been established by the usual criteria. In 4 patients, identification of these crystals was the first laboratory evidence of gout.

In order to further characterize these particles, two methods have been employed in addition to their morphologic appearance. Microscopic examination with polarized light has shown the urate crystals to be negatively birefringent with extinction on the long axis of the crystal. Digestion by incubation with uricase has consistently destroyed these crystals.

Comparison of the results obtained by ordinary light microscopy with those obtained by polarized light revealed that the percentage of positive identification was raised from 61 to 83%. Also two specimens contained numerous crystals by ordinary light which were not birefringent by polarized light and which were not digested by uricase. One of these specimens was from the knee of a patient with classical acute gouty arthritis and the other was from a case of atypical osteoarthritis of knees and shoulders. This finding raises the possibility of an hitherto unrecognized metabolic abnormality which can produce the syndrome of gout.

The characteristics of urate crystals by polarized light appear to be specific. No other particles were encountered in examination of over fifty fluids from patients with other varieties of joint disease which were rod shaped and negatively birefringent.

Our experience would indicate that this rapid, simple test is a valuable aid in establishing the diagnosis of gout.

Abstract 15

Hyponatremia and Renal Sodium Wasting in Patients with Malfunction of the Central Nervous System. Martin Goldberg, M.D., and Joseph S. Handler, M.D.

The authors report seven patients in whom an apparently inappropriate secretion of antidiuretic hormone was associated with disease of the central nervous system, hyponatremia, and excessive renal sodium loss.

The mean age for the group was 69 years, the youngest being 60. Manifestations of central nervous system abnormalities were present in each patient and included disorientation, seizures, coma, hemiparesis, and ataxia. The basic disease processes were primary intracranial lesions (neoplastic or vascular) or were secondary to toxic or metabolic factors such as general anesthesia, depressant drugs, alcoholism, or anoxia. In this age group it is conceivable that underlying cerebral vascular degenerative changes were contributory. There was no clinical evidence of classical salt depletion with dehydration, hypotension, or azotemia. Edema or ascites was not present. Stigmata of adrenal insufficiency or evidence of primary renal disease were not observed. In each case serum sodium concentration reached values lower than 123 mEq./L. The hyponatremia was associated with normal BUN, low serum osmolality ($<$ 260 mOsm./kg.), and a significantly higher urine osmolality ($>$ 280 mOsm./kg.). Three patients were evaluated in greater detail. When daily water intake was greater than 2500 cc., hyponatremia was only partially corrected by administration of large amounts of sodium as the sodium load was rapidly excreted. Restriction of fluid intake to less than 1500 cc. per day was followed by progressive rise in serum sodium concentration, even while on a low sodium diet.

One patient showed almost complete reversal of her neurological manifestations as serum sodium reached normal values, but she did not subsequently develop hyponatremia on unrestricted water intake and a normal sodium diet. While on a restricted water intake, one patient improved clinically and was discharged from the hospital. Mental confusion and hyponatremia associated with a hypertonic urine recurred four months after discharge when water intake was increased. Autopsy in three patients disclosed normal kidneys and adrenal glands. On examination of the brain in two cases, a ruptured aneurysm was present in one

case, and multiple areas of cerebral infarction were found in the other case.

In each case urine was hypertonic while serum osmolality was abnormally low, suggesting that antidiuretic hormone activity was present but that secretion of the hormone was not regulated by osmotic stimuli (1–4). The exact nature of the abnormal stimulus has not been delineated.

REFERENCES

1. Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, O.: Evidence in man that urinary electrolyte loss induced by pitressin is a function of water retention. J. Clin. Invest. **32:** 868, 1953.
2. Berliner, R. W., and Davidson, D. G.: Production of hypertonic urine in absence of pituitary antidiuretic hormone. J. Clin. Invest. **35:** 690, 1956.
3. Schwartz, W. B., Bennett, W., Curelop, S., and Bartter, F. C.: Syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am. J. Med. **23:** 529, 1957.
4. Schwartz, W., Tassel, D., and Bartter, F. C.: Further observations on hyponatremia and renal sodium loss probably resulting from inappropriate secretion of antidiuretic hormone. New Eng. J. Med. **262:** 743, 1960.

Abstract 16

Ganglion Blocking Agents used in Combination with Rauwolfia and Chlorothiazide for the Treatment of Hypertension. Albert N. Brest, M.D., and John N. Moyer M.D.

It now appears that the use of ganglion blocking compounds given in combination with Rauwolfia and chlorothiazide is the most effective method of blood pressure reduction in patients with moderate and severe hypertension. The majority of side effects encountered with the ganglioplegic drugs are due to an associated blockade of the parasympathetic ganglia; however it is usually possible to reduce the blood pressure significantly in the upright position before the side effects due to parasympathetic blockade become prohibitive.

The rationale for the concurrent use of Rauwolfia and chlorothiazide is a pharmacologic one. These agents potentiate the antihypertensive effectiveness of the ganglioplegic drugs and they also diminish the incidence and severity of the accompanying side reactions.

Subjective improvement occurs in most instances after a significant blood pressure reduction has been accomplished. In addition, associated vascular deterioration is generally arrested and objective improvement is often noted. Cardiac failure is frequently improved; and electrocardiographic changes tend to revert toward normal (except in those patients showing infarctions). Grade 3 or 4 fundi usually improve, and papilledema is especially prone to clear with therapy. Improvement in renal function is variable. When there is ample reserve, the effect of ganglionic blockade in depressing renal vasospasm often enhances renal function. On the other hand, kidney function may be further impaired when the renal status is borderline. Nevertheless the hypertensive patient with a high BUN is not without hope since reduction of blood pressure in some cases increases renal function and the BUN returns to tolerable levels.

The most important aspect of therapy with ganglion blocking agents is effective dose titration. The dosage requirement of different patients is often quite variable; therefore an "average" dose is frequently ineffective in individual instances. In addition, many patients require special adjustments depending on their mode of living and variability in environmental stresses.

Certain ganglioplegic drugs offer advantages over the others, particularly with regard to their ease of titration. In our experience, mecamylamine and pentolinium have been the easiest to use clinically and have given the best results. Mecamylamine is particularly advantageous because of its greater potency and complete absorption from the gastrointestinal tract.

Abstract 17

Myocardial Infarction: Factors in Delayed Recovery. William L. Winters, Jr., M.D., Barney Dlin, M.D., H. Keith Fischer,

M.D., Samuel B. Hagner, M.D. and George W. Russell, M.D.

An acute myocardial infarction presents to the human system a stress which may elicit a wide spectrum of physiologic responses. The sequential changes of these physiologic reactions are equally well recognized. The presence of troublesome arrhythmias, congestive heart failure, persistent angina pectoris, post-myocardial infarction syndrome, hand-shoulder syndrome are accepted as sequelae, undesirable as they may be, which may delay recovery for weeks or months.

A second type of response, just as important and just as varied in its manifestations, is the emotional reaction. This has been little studied until recent years partly because of the unusual symbolic relationship between the heart, life and death. Yet an abnormal reaction in this sphere may delay recovery just as surely as persistent angina pectoris. Proper understanding by physicians of these reactions and their relation to the pre-coronary personality may greatly reduce the 25–40% of post-coronary patients who presently fail to make adequate adjustments despite medical permission to work.

The data presented in abstracted form from material collected over an 8 year period by a myocardial infarction study group composed of internists and psychiatrists and headed until recently by the late Dr. Edward Weiss. The principle purpose of this group was to study the emotional factors before, accompanying and following an acute coronary occlusion. The subject matter consisted of 70 hospitalized patients. The first 43 were selected at random. The next 27 were selected for having their first coronary occlusion without prior personal or family history of cardiovascular disease. Interviews were conducted by the psychiatrists starting on an average of 9 days following the acute onset of the illness and proceeded for from 3 to 12 interviews per patient. Data obtained was reviewed in research seminars by the entire group and master data sheets prepared for each patient. In this manner it was hoped the results would prove useful to the practicing physician as well as the psychiatrist. Early interviewing in this manner permits more objective evaluation of the roles of unconscious feelings and attitudes in relation to the heart disease before dilution of the emotional reactions occurs by the passage of time.

Four major subdivision of the post-coronary emotional reaction evolved. I. Normal reaction: The patient accepts the reality of the attack and its implications. A normal anxiety response is observed usually with mild depression. These improve with improvement in the physical state. This group embraced the largest number of patients. II. Psychoneurotic reaction: These patients accept the reality of the attack and its implications, but personality and ego are not sufficiently strong to prevent the occurrence of extreme anxiety, chronic fears, depressive and regressive reactions manifested by hypochondriasis, agitation, rebellion and stubbornness. III. Denial of illness: The patient rejects the reality of the attack and distorts the facts and implications. The personality compensates, though anxiety may be present, but denial dominates the clinical picture. Surprisingly physicians often respond in this manner. IV. Psychopathology: The patient rejects reality of the attack. He distorts the facts and implications. The personality decompensates and manic depression, paranoia, and beserk behavior appears.

The pre-coronary personality undoubtedly contributes largely to the type of reaction observed, but iatrogenic influence of excessive caution concerning physical activity, work, sex without correlation to the type of emotional reaction experienced contributes its share. The psychological delay in recovery may be distinctly abbreviated by educating the patient and physician to the relationship of the soma and the psyche following an acute coronary occlusion.

REFERENCES

1. Weiss, E., Dlin, B., Rollin, H. R., Fisher, H. K. and Bepler, C. R.: Emotional Factors in Coronary Occlusion. I. Introduction and General

Summary. A.M.A. Archives Int. Med. **99**: 628–641, 1957.

2. Dlin, B., Fisher, H. K., Hagner, S. B., Russell, G. W., and Winters W. L., Jr.: Emotional Factors in Coronary Occlusion. II. Psychology of Delayed Recovery—Clinical Considerations. In press.

Abstract 18

Serum Enzymes with Acute Arterial Occlusion of Dog Limbs. Ugo Manzoli, M.D., Raymond Penneys, M.D., Samuel Bellet, M.D., and Leonard Feinberg, Ph.D.

These experiments were done to relate levels of the (systemic) serum enzymes, glutamic oxalacetic transaminase (G.O.T.), lactic dehydrogenase (L.D.H.) and isocitric dehydrogenase (I.C.D.), to ischemia of the animal limb, in the same manner that they have been related to ischemia of the myocardium.

In the first group of experiments, embolism of a hind limb was produced in 16 dogs by the injection of a lycopodium suspension into the femoral artery. This resulted in severe, ischemic damage to the limb, progressing to gangrene in 13 of the 16 animals. All three enzymes increased within four hours after embolization, much before the appearance of gangrene, and remained so during the 96–144 hour observation period. The greatest increase was in G.O.T., which rose from approximately 40 units (average) before embolization, to 1,000 units at 24–48 hours after embolization. The next greatest increase was in I.C.D., which rose from 100 to 600 units, at 12–24 hours, and the least was in L.D.H., from 100 to 300 units, at 12–24 hours. Sham operations done on four dogs produced no significant rise in enzyme levels, demonstrating that embolization, per se, was responsible for these increases in serum enzymes.

A second set of experiments, still in progress, was done to study the effect of milder degrees of ischemia of the limb. The femoral artery was occluded temporarily for one hour and for three hours in two groups of six animals each; in neither group was there any evidence of serious damage to the limb. Levels of the two enzymes measured, G.O.T. and I.C.D., remained essentially unchanged during the 24 hour observation period after occlusion.

Levels of certain serum enzymes, then, are related to the degree of ischemic damage of the limb. Such enzyme determinations probably reflect the degree of damage of the deeper tissues of the limb, something not provided by the routine clinical examination, and should therefore be of value in the management of patients having peripheral arterial disorders.

Abstract 19

A New Defect in Thyroid Hormone Synthesis. Angelo M. Di George, M.D.

In the past decade, rapid progress has been made in the delineation of various biochemical anomalies of the thyroid gland. Five distinct and reasonably well-defined defects of thyroid hormone synthesis have been described in association with sporadic goitrous cretinism. These are:

1. *Absence of iodide concentrating mechanism.* The first and only instance was described by Stanbury and Chapman (1), a few months ago.

2. *Failure to produce organic iodine.* This defect was first described in 1950 and is presumed to result from a defect in the peroxidase enzyme system (2).

3. *Failure to couple iodotyrosines to form iodothyronines.* Described initially in 1955 and believed to result from an inability of the thyroid gland to couple monoiodothyrosine and diiodothyrosine into thyroxine and triiodothyronine (3). Convincing proof of existence of a coupling enzyme is still lacking.

4. *Absence of dehalogenase enzyme.* Described in 1953 by McGirr and Hutchison (4). An inability to deiodinate monoiodotyrosine and diiodotyrosine results in the appearance of these compounds in the blood and urine.

5. *Syndrome of congenital goiter with butanol insoluble serum iodine.* Described in 1956 by Di George and Paschkis (5). The thyroid secretes an abnormal iodinated compound into the blood which is calorigenically inert. The basic biochemical defect underlying this disorder is not established.

More recently Rupp, Chavarria and Pasch-

kis (6) have described a euthyroid patient with a goiter and defective synthesis of thyroid hormone. The only circulating thyroid hormone demonstrable in this subject was triiodothyronine. Werner and co-workers (7) have subsequently reported a 14 year old girl with a nodular goiter who had a similar defect.

The present report is concerned with studies performed on a six year old child who has yet another defect distinct from all of those described above. Thyroid enlargement made its appearance at three years of age. Growth and development were normal. Laboratory studies supported the clinical judgment that the child was euthyroid. Serum protein bound iodine levels on repeated occasions ranged between 1.9 and 2.8 mcgm. per cent. Radioactive iodine uptake by the thyroid gland after 24 hours on three occasions was 65%, 51% and 66%. Chromatographic examination of I^{131} labeled circulating thyroid hormones by J. J. Rupp revealed the presence of triiodothyronine and diiodotyrosine. Thyroidectomy was performed. The gland weighed 100 grams and histologic examination showed hyperplasia and adenomatous changes.

On the basis of current knowledge of thyroid hormone synthesis, these findings cannot be explained without invoking more than one mechanism of disordered thyroid function.

REFERENCES

1. Stanbury, J. B., and Chapman, E. M.: Congenital Hypothyroidism with Goitre. Absence of an Iodide Concentrating Mechanism. Lancet **1:** 1162, 1960.
2. Stanbury, J. B., and Hedge, A. N.: A Study of Familial Goitrous Cretins. J. Clin. Endocrinol. **10:** 1471, 1960.
3. Stanbury, J. B., Ohela, K., and Pitt-Rivers, R.: The Metabolism of Iodine in two Goitrous Cretins Compared with that in two Patients Receiving Methimazole. J. Clin. Endocrinol. **15:** 54, 1955.
4. McGirr, E. M., and Hutchison, J. H.: Radioactive Iodine Studies in non-endemic Goitrous Cretins. Lancet **1:** 1117, 1953.
5. Di George, A. M., and Paschkis, K. E.: Sporadic Hypothyroidism Associated with Goiter. J. Clin. Endocrinol. & Metab. **17:** 645, 1957.
6. Rupp, J. J., Chavarria, C., Paschkis, K. E., and Chublarian, E.: The Occurrence of Triiodothyronine as the Only Circulating Thyroid Hormone. Ann. Int. Med. **51:** 359, 1959.
7. Werner, S. C., Row, V. V., and Rodichevich: I. Nontoxic Nodular Goiter with Formation and Release of a Compound with the Chromatographic Mobility Characteristics of Triiodothyronine. J. Clin. Endocrinol. & Metab. **20:** 1313, 1960.

Abstract 20

The Effect of Freezing on the Production of Antibody by Bone Marrow. Irwin L. Stoloff, M.D.

Mammalian cells of many types have been successfully preserved by freezing in a glycerol medium. The widest clinical application to date of this method has been the preservation of whole blood and bone marrow. Viability studies which have been reported using frozen material indicate that the majority of cells survive and, presumably, resume normal function after rapid thawing. This report is concerned with the suppressive effect of freezing on cells engaged in the production of antitoxin.

Methods

A. It has been established that the bone marrow of hyperimmunized mice can produce sufficient tetanus antitoxin after transfer to irradiated hosts of the same strain to protect the animals against a lethal dose of tetanus toxin. The technique of immunization, irradiation, bone marrow transfer, and detection of antitoxin production by donor cells has been described earlier (1).

B. Bone marrow cells were preserved in 15% glycerol by the Polge-Smith-Parkes technique of gradual freezing to −79°C.

Results

Hosts receiving approximately equal numbers of marrow cells from hyperimmunized donors were compared according to their susceptibility to tetanus toxin. The results are summarized as follows.

1. Both fresh and frozen marrow suspensions protected hosts against a lethal dose of total-

body irradiation. Control animals all died within thirty days of irradiation.

2. Fresh marrow protected hosts challenged with tetanus toxin. Mice receiving frozen cells from similarly immunized donors were not protected against toxin and behaved no differently to toxin than controls receiving no cellular protection.

Discussion

The preservation of murine bone marrow by gradual freezing in glycerol has been described by previous authors (2). In the present experiments, restoration of cellular function after thawing was adequate to protect mice against the lethal effects of total-body irradiation. The suppressive effect of freezing in glycerol on the capacity of bone marrow to produce antitoxin after proper stimulation indicates that not all of the marrow cells are restored to normal function. In contrast, fresh marrow from hyperimmunized donors protected hosts against both irradiation and tetanus toxin.

The reason for the lack of protection against tetanus toxin by preserved marrow is not apparent in these experiments. It is possible that the method of preservation selectively suppresses antibody-producing cells without damaging the remainder of the marrow cells. Alternatively, all the elements of marrow may be equally suppressed but a larger percentage of antibody-producing cells may be required to protect hosts against tetanus toxin then the percentage of marrow cells needed to protect the host against irradiation. Either possibility would account for the protective effect of preserved marrow against irradiation and the lack of protection against tetanus toxin while fresh marrow protected hosts against irradiation and tetanus toxin. Further work is in progress to clarify this question.

REFERENCES

1. Stoloff, I. L.: The Production of Antibody by Transferred Bone Marrow. J. Immunol. **85:** 304–308, 1960.
2. Schwartz, I. R., Repplinger, E. F., Congdon, C. C., and Tocantins, L. M.: Transplantation of Bone Marrow after Preservation at −70°C. J. Appl. Physiol. **11:** 22–24, 1957.

Abstract 21

Pyridoxine Deficiency in Hyperthyroidism. Michael G. Wohl, M.D., Howard A. Levy, M.D., Anton Szutka, Ph.D., and G. Maldia, M.D.

Among the main micronutrients whose quantitative requirements are elevated in experimental hyperthyroidism are certain of the B complex vitamins. In view of the fact that pyridoxine is involved in a great many enzymatic reactions, it appeared desirable to investigate pyridoxine metabolism in hyperthyroidism in man. Fourteen patients with clinical and laboratory signs of hyperthyroidism and fourteen non-hyperthyroid patients (controls) were studied.

The increased excretion of xanthurenic acid after tryptophan load and its correction by pyridoxine served as an index of relative pyridoxine deficiency. The hyperthyroid group and the control group were comparable with respect to both mean and standard deviation in pre-tryptophan level of xanthurenic acid excretion with means of 7.3 and 5.1 mg./24 hr., respectively. Following tryptophan load, the mean increase for the hyperthyroid group was significantly greater than that for the control group (probability of 'T' less than 0.05), so that the former reached a significantly higher mean level of excretion (71.9 vs. only 15.4 mg./24 hr.). After pyridoxine, the hyperthyroid group showed a greater decline in xanthurenic acid excretion than the controls. The biochemical response to the administration of pyridoxine with improvement in the derangement of tryptophan metabolism would tend to indicate that the nutritional status of hyperthyroid patients with respect to vitamin B6 is subnormal.

It is noteworthy that two of our hyperthyroid patients, whose main presenting symptom was extreme weakness of the quadriceps femoris muscle group, showed pyridoxine deficiency. Upon intramuscular administration of 50 mg. of pyridoxine daily for a period of 5 days, there was marked improvement in their muscle weakness.

Abstract 22

THERAPY OF SERIOUS CARDIAC ARRHYTHMIAS FOLLOWING ACUTE MYOCARDIAL INFARCTION. Leonard S. Dreifus, M.D., Theodore Oslick, A.B., and William L. Likoff, M.D.

A high immediate mortality has been associated with acute myocardial infarction in the presence of cardiac arrhythmias.

Review of 248 consecutive acute myocardial infarctions revealed 41 instances in which there was an associated serious cardiac arrhythmia. Of this group 13, died with their arrhythmia.

Atrial arrhythmias were associated with a 47% immediate mortality as opposed to 27% with uncomplicated myocardial infarction. Digitalis or its glycosides were unquestionably the drugs of choice for these arrhythmias.

Ventricular tachycardia was associated with a 60% immediate mortality in spite of antiarrhythmic therapy. Failure of response to procaine amide was a sinister sign as other agents (quinidine, KCl, and zylocaine) were invariably ineffective. On the other hand, if the patient survived the initial complication, long term survival was equally as good as those with an uncomplicated infarction.

Mortality increased with the magnitude of A-V block. Isoproternol enhanced impulse formation in incomplete A-V block by acceleration of supraventricular pacemakers as well as by improvement of A-V conduction. Concentration should never exceed 3–4 mcg/ml. and rapid administration should be avoided as undue acceleration of ventricular impulse formation may occur culminating in ventricular tachycardia.

Steroids were successful in a few instances in enhancing A-V conduction in the presence of transitory A-V heart block. Advanced 2nd and 3rd degree A-V block should be continuously monitored because of instability of subsidiary (A-V nodal or ventricular) pacemakers. An electrical pacemaker should be set to fire after 3 seconds of asystole.

Non-paroxysmal nodal tachycardia may masquerade as a simple supraventricular arrhythmia. Inappropriate use of digitalis may permit the patient to die with this rhythm. Procaine amide or potassium appear equally effective in terminating this mechanism.

Abstract 23

MODE OF ACTION OF QUINACRINE INHIBITION OF LE CELL FORMATION. Neilon Neilson, M.D., and John Lansbury, M.D.

More and more evidence is accumulating to show that the antimalarial drugs exert a long range, favorable action against certain rheumatic diseases, notably rheumatoid arthritis and the more chronic forms of systemic lupus erythematosus. The antimalarials are likewise known to be capable of suppressing LE cell formation *in vitro*. The present study on the mode of action whereby LE cell production is blocked by these drugs was undertaken in the hope that it might lead to a fuller understanding of the pharmacological action of these drugs against the above diseases.

LE formation is the end result of these separate links in a chain of events. These are as follows: 1) The LE serum factor (gamma globulins) is able to penetrate dead or dying leukoyctes. 2) It then combines with the nucleoproteins of their nuclei to form an "LE body" which is extruded from the cell. 3) The LE body is then phagocytosed by a viable polymorphonuclear leukocyte to form the LE cell. Thus, inhibition of LE cell formation by an antimalarial drug could theoretically be due to: 1) Neutralization of the LE serum factor: 2) Protection of the nucleus against this factor and 3) Inhibition of phagocytosis of the LE bodies which are formed by the interaction of LE serum and leukocyte nuclei.

Preliminary experiments using Quinacrine (Atabrine) indicate that during electrophoresis this drug is not bound to the gamma globulins; in smears of leukocytes it is found to be concentrated mainly in the cytoplasm and only slightly in the nuclei and was only faintly identifiable in nuclear bodies, from which it could be easily separated by washing. On the other hand, phagocytosis was almost entirely inhibited by concentrations of 0.4 mgm. per

milliliter of Quinacrine. These findings are not conclusive but point towards inhibition of phagocytosis as the most likely point at which LE cell formation is blocked.

Three additional experiments were then devised, as follows:

1. LE serum treated with Quinacrine was used to test for LE cell production using the Snapper Nathan ring technique.

2. Leukocyte nuclei were treated with Quinacrine and used as ready-made LE bodies, then reacted with active LE cell serum, and again tested for LE cell formation.

3. LE serum and leukocytes were interacted to form LE cell bodies but then quickly frozen to prevent phagocytosis. Subsequently, a suspension of leukocytes containing various concentrations of Quinacrine were used to test for phagocytosis and therefore LE cell production.

No evidence for blocking of the LE cell serum factor nor of protection of leukocyte nuclei against this factor was obtained. On the other hand, no LE cells were formed when live phagocytizing leukocytes were exposed to Quinacrine in concentrations of 0.4 mgm. per milliliter.

We conclude that LE cell formation is blocked by Quinacrine at the level of inhibition of phagocytosis rather than at the serum factor level or the nuclear level. This does not explain the action of antimalarials in inhibiting the activity of rheumatoid arthritis or SLE unless injury to leukocytes is somehow involved in the process. Blocking of LE cell formation might conceivably be useful as a screening device for antirheumatic drugs provided the site of action is determined by procedures such as we have used.

Abstract 24

TREATMENT OF INTRACTABLE HEART FAILURE IN THE PRESENCE OF COMPLETE AV-HEART BLOCK BY THE USE OF THE INTERNAL CARDIAC PACEMAKER: REPORT OF A CASE. Otto F. Muller, M.D., and Samuel Bellet, M.D.

A 73 year old man was presented who had a six year history of coronary artery disease with repeated episodes of myocardial infarction. Within a period of five years, the patient was admitted to the hospital on ten different occasions because of episodes of acute pulmonary edema and congestive heart failure. He responded well to treatment with digitalis, diuretics, and repeated thoracocenteses, and lost between 12 and 25 pounds of weight during each hospitalization. During the last year of his illness, he developed a temporary complete AV-heart block which disappeared when digitalis was discontinued. However, a few weeks later he showed a persistent AV-heart block with a ventricular rate of between 22 and 36/minute, became refractory to all conventional therapeutic measures and finally was so incapacitated that he was unable to leave the bed for more than a few minutes. In an attempt to increase the cardiac output by raising the heart rate, a stimulating catheter electrode was inserted into the right external jugular vein, passed through the right auricle into the right ventricle and connected to a transistorized internal cardiac pacemaker. The ventricular response was at first irregular, but later stabilized with a 1:1 response at a rate of about 68 beats per minute. The patient's congestive heart failure began to improve on the second day and he was allowed out of bed and was able to walk to the bathroom on the third day. The clinical improvement was remarkable and within 20 days of continuous pacemaking the patient lost 33 pounds of weight and became compensated so that "he felt better than he had for years."

Due to the increased activity of the patient the catheter electrode became dislodged and failed to yield regular stimulation so that it was removed on the 21st day of pacemaking. The patient's cardiac rate remained at 40 to 48 beats per minute for 10 days, but slowly the previous signs and symptoms of congestive heart failure returned and he gained weight rapidly. Reinsertion of the electrode was contemplated but the patient died suddenly of an acute myocardial infarction, 4 weeks after removal of the pacemaker. Postmortem exami-

nation revealed an old extensive arterolateral myocardial infarction with aneurysmal dilatation of the left ventricular wall and an acute extension into the surrounding myocardium. Thrombi or emboli were not found anywhere. There was generalized acute congestion of the organs.

In this patient the use of the internal cardiac pacemaker was shown to be of considerable value in the treatment of severe congestive heart failure in the presence of persistent low heart rates, intractable to all conventional therapeutic measures. The increase in heart rate from 22 to approximately 68 beats per minute led to marked clinical improvement by increasing the cardiac output and coronary blood flow, both of which were very low in this patient not only due to the presence of complete AV-heart block but also due to extensive coronary sclerosis and myocardial infarction.

Abstract 25

THE USE OF DISODIUM EDTA IN THE TREATMENT OF OBLITERATIVE PERIPHERAL VASCULAR DISEASE. J. Roderick Kitchell, M.D.

Until the recent advent of vascular surgery which allowed for replacement or reconstruction of diseased arteries, no definitive therapy for peripheral vascular diseases was available. The so-called vasodilator drugs are notoriously ineffective in terms of disease progression and are no more than a token measure. Sympathectomy in most cases is only palliative and its effect short lived. With replacement surgical techniques obstructive arterial disease is corrective in some cases but the number of suitable candidates for this type of revascularization has proved less than would be hoped for. As experience has grown, it is apparent that only very selected cases should undergo such therapy.

It is our purpose to describe a new and different approach to this problem and to briefly discuss our experience with this method.

We have treated 25 patients with PVD during the past 3 years by means of chelation techniques. You are familiar with chelation as a therapy for lead poisoning wherein the chelating agent is able to bind lead, rendering it physiologically inactive, and allowing for its excretion from the body. This principle has been applied as a therapy for other heavy metal poisonings and when it became apparent that metals as calcium, iron, and copper could be similarly bound, chelation was attempted in a variety of other diseases. Our original interest concerned the removal of calcium in coronary artery disease and Meltzer and I reported our preliminary observations with this work 2 years ago. While the results were encouraging it became evident that more carefully conceived and controlled studies would be needed before a valid conclusion could be reached. We then embarked on a large scale investigation of the effect of chelation on calcareous cardiovascular diseases. This study is currently in progress at the Presbyterian Hospital of Philadelphia, being sponsored by the Hartford Foundation.

Our original premise was that by being able to bind calcium with the chelating agent disodium EDTA we might beneficially reduce intimal plaque formation and increase blood flow. It has been shown that each gram EDTA can chelate 108 mg. calcium.

Patients with advanced occlusive arterial disease were chosen as subjects for this study. Prior to therapy we attempted to define the degree of vascular impairment with the following examinations:

1. Segmental and digital plethysmography. With the use of the newer apparatus for this purpose which now allows standardization of the pulse curves (not possible with older machines) we have excellent controls for comparative purposes in terms of blood flow and volume flow.

2. The treadmill has proved to be very valuable to estimate the severity of vessel disease from a functional standpoint.

We have designed a treadmill to meet our needs. The patient must walk at a known rate (1.5 m.p.h.) on a 7° inclined belt. The distance the patient can walk prior to claudication (or before and after therapy) can be accurately recorded.

3. Arteriograms have been made prior to treatment in many patients but this is a less sensitive index of improvement than the previous methods.

4. Other studies included skin temperatures, photographs of skin and hair distribution of the feet and oscillometric measurements.

After evaluation, patients began a course of chelation. This was accomplished in a special clinic built for our purposes. The subjects were outpatients.

The EDTA is administered intravenously. We use 3.0 gm. of this agent in 500 cc. saline or glucose which is administered over a 2½–3 hour period. The patients are under constant nursing supervision. They receive these treatments usually on alternate days (3 times a week) until they have received 20 such infusions. A rest period of 6–8 weeks follows. For reasons we do not yet understand the maximum improvement does not occur until the rest period and there is generally no improvement during the period of therapy.

Depending on the results of this course of treatment, additional courses of EDTA follow as needed. We have one patient who has received 100 infusions thus far.

Studies are repeated after each course and comparison made with the baseline studies.

At this point in our work it would not be wise to present our formal data and draw a conclusion since the study is not complete—but we can give our general impression. It appears as if some patients have been obviously helped. Their plethysmograms show better pulsations. There is greater blood flow. They can walk better. In some, claudication has disappeared. Arteriograms have shown improvement. The clinical appearance of the extremities has improved. In several cases callus formation, present for years on the feet, has cleared. Other patients (the minority) have not been helped as spectacularly. Two have gone on to amputation but even in these people there has been a surprising absence of calcinosis in the vessels. It would be fair to say that the *degree* of improvement that has occurred in the patients that have been helped is far greater than could be anticipated by any other medical means of treatment now available.

We do not know if all patients would improve if therapy were started early enough nor do we know if only certain types of peripheral diseases are amenable to treatment. It is our impression that the patients with medial sclerosis (Mönckeberg type) and the Leriche syndrome type with calcification in the major vessels, are likely the poorest candidates for this treatment.

Our thinking about the mechanism accounting for improvement has changed as our work has progressed. We originally felt that calcium removal was the key to the problem, but it would now appear that more sophisticated concepts are involved and that chelation may be affecting certain enzyme systems or lesser trace metals to produce the end results.

Summary. We have used Na_2EDTA therapy on 25 cases of peripheral vascular disease over periods up to three years. Results have been good to excellent in those with arteriosclerosis involving the smaller vessels. Results are not so spectacular in the types with large vessel occlusions, (Leriche syndrome and thrombosis in iliofemoral popliteal areas), or with medial sclerosis (Mönckeberg type). Methods of diagnosis, baseline studies, and methods of judging progress are briefly discussed. It is not yet possible to be sure why these patients did or did not benefit.

Abstract 26

Implication of Nickel as a Pulmonary Carcinogen in Tobacco Smoke. F. William Sunderman, M.D., Ph.D., and F. William Sunderman, Jr., M.D.

High incidence of respiratory cancer has been recognized in industrial workers who have been chronically exposed to the inhalations of nickel carbonyl or nickel dust. For a number of years our laboratory has studied the hazards of such exposures. Recently we have reported the experimental induction of pulmonary cancers in rats subjected to 30 minute inhalations of nickel carbonyl in concentrations of 4 parts per million thrice weekly for a period of

one year. These neoplasms were not observed until two or more years after the initial exposure.

Measurements have been made of the nickel content in cigarettes and of the partition of nickel in the ash and butt, main-stream and side-stream smokes. Six common brands of American cigarettes contained from 1.59 to 3.07 mcgm of nickel per cigarette. Twenty per cent of the total nickel was recovered from the main-stream smoke. Similar measurements were made on cigar and pipe tobaccos.

It has been estimated that the amount of nickel inhaled in one year by a heavy cigarette smoker is approximately three times the amount of inhaled nickel which we have previously reported to be carcinogenic for rats—an animal notably resistant to the induction of pulmonary cancer.

In the light of these investigations it is our considered opinion that attempts should be made to remove nickel from tobacco smoke.

Abstract 27

Biliary Dyskinesia—Discussion of Diagnosis. Franz Goldstein, M.D.

Biliary dyskinesia is a term apparently first used by Westphal to denote a widespread disruption of autonomic nervous activity leading to functional disturbances of gallbladder evacuation. Both a hypertonic and a hypotonic type of dyskinesia were originally postulated but there is little evidence for the existence of hypotonic dyskinesia as a clinical syndrome. Symptoms of hypertonic biliary dyskinesia may be produced by partial obstruction of the biliary passages due to organic causes (mechanical dyskinesia) or by functional disturbances in the neuromuscular mechanism which normally controls the simultaneous contraction of the gallbladder and relaxation of the sphincter of Oddi (functional dyskinesia). Although the presence of biliary dyskinesia can be suspected from the rather characteristic symptomatology, diagnostic proof is difficult to obtain by conventional laboratory and radiologic methods. Much confusion has arisen concerning the meaning of biliary dyskinesia and the term has been erroneously applied to, or equated with, flatulence, aerophagia and the irritable bowel syndrome. On the other hand, patients with true biliary dyskinesia have been denied proper treatment and have been falsely labeled as psychoneurotics.

Two patients with typical symptoms of biliary dyskinesia were studied. Both were young women who complained of early postprandial right upper quadrant abdominal pains of one and ten years' duration, respectively. The gallbladder was palpable and tender in one patient; her pain could be temporarily relieved with sublingual nitroglycerine. Blood chemical tests were normal except for a slight bilirubin elevation in one patient. The routine cholecystograms revealed good filling of the gallbladder. The cholecystograms were repeated and biliary drainage was performed, using intravenous cholecystokinin as the stimulant of gallbladder evacuation. Normally, gallbladder contraction and evacuation begins within one to two minutes after the injection of cholecystokinin and is completed within ten minutes. A marked delay in the appearance of gallbladder bile was observed on biliary drainage, as compared to the normal response. Serial roentgen films of the gallbladder taken at approximately three minute intervals after the injection of cholecystokin revealed delayed and incomplete evacuation of the gallbladder in each patient. The injections of cholecystokinin reproduced both patients' spontaneous pains. Both patients were subsequently operated on and each found to have partial mechanical obstruction to the outflow of bile by bands and adhesions. One patient had, in addition, a hypertrophied sphincter of Oddi. Following cholecystectomy and sphincterotomy, both patients have remained free of symptoms during follow-up periods of over one year.

The use of intravenous cholecystokinin in combination with biliary drainage and cholecystography is recommended as a simple means to detect delayed evacuation of the gallbladder in suspected cases of biliary dyskinesia.

Abstract 28

THE NEUROSURGICAL TREATMENT OF SPONTANEOUS INTRACRANIAL HEMORRHAGE (WITH SPECIAL REFERENCE TO "CEREBRAL APOPLEXY"): AN EVALUATION OF LONG-TERM POST-OPERATIVE RESULTS. Michael Scott, M.D.

In 1952 the writer reported operative results in 30 patients with spontaneous intracranial hemorrhage (1). This is a follow-up of the survivors (2). Seventy-five per cent of the 30 patients were between 40 and 66 years of age.

Table I lists the pre-operative findings.

TABLE I

SUMMARY OF PRE-OPERATIVE CLINICAL FINDINGS IN THIRTY PATIENTS WITH SPONTANEOUS INTRACRANIAL HEMORRHAGE

Clinical Findings	Patients	
	No.	%
History		
Hypertension	18	60
Severe headaches	22	73
Nuchal Rigidity (117 patients examined)	10	58
Sensorium		
Awake	3	10
Drowsy	13	43 } 90
Stupor or coma	14	47 }
Dilated pupil on side of hemorrhage	7	23
Choked disk	2	7
Visual field defect	6	20
Motor aphasia	4	13
Mixed aphasia	3	10
Hemiparesis	7	23 } 80
Hemiplegia	17	57 }
Decerebrate rigidity	5	17
Negative result of Wassermann test (25 patients examined)	25	100
Spinal fluid (26 patients examined)		
Pressure elevated	24	92
Red blood cells	20	77
Roentgenographic evidence of pineal gland shift (22 patients, pineal gland calcified, 11)	11	100

Indications for Surgery

Operation was indicated if there was deterioration of conscious levels and progression in neurologic deficit.

I avoided operating on extensive hemorrhage in the dominant internal capsule because if the patient survived, the added burden of the motor aphasia to the hemiplegia seemed unbearable. Coma per se was not a contraindication and although the operative mortality was highest with this complication, the best long-term result occurred in a comatose patient. Surgery was not done in those with advanced cardiac, renal, or pulmonary disease.

The hematomas were evacuated in all cases and biopsy was done in 29. An aneurysm was found in one; arterial rupture without aneurysm in 3; brain tumor in two—chorioepithelioma and melanoma; no cause for the bleeding was found in 24.

Mortality

Eleven patients died. The operative mortality was 37%. Nineteen were discharged and in the 1952 report, the shortest follow-up was 3 months and the longest 7 years.

The location of the clot was an important factor in the patient's survival and his subsequent neurolgic deficit:

Hemorrhage into the Internal Capsule (20 Patients)

Ten died in the hospital; an operative mortality of 50%, or 40% if the two tumor cases are excluded. Ten were discharged. Six died: 3 months, 5 months, 5 months, 4 years, 4 years, and 6 years later.

Four are still alive (10, 11, 12, and 12 years).

Hemorrhage into the Temporal Lobe and Its Adjacent Area (7 Patients)

All survived surgery. Three subsequently died and one could not be followed; three are still alive 9, 12, and 13 years following surgery.

Hemorrhage into the Subdural Space (3 Patients)

One died 20 days post-operatively from an epidural hemorrhage; one died 12 years later

from a heart attack and the 3rd is alive 13 years later.

Post-Operative Convulsions

Six patients (32%) of the nineteen who survived surgery have had one or more convulsions favorably controlled with anti-convulsants.

Autopsy Findings

Autopsies were done in 10 of 20 deaths. Hematoma into a metastatic brain tumor was found in two. Persistent hemorrhage with softening and edema was the most common cause for death. Pontine and cerebral hemorrhage occurred in 3 patients.

One patient who survived removal of a large temporal lobe hematoma died 9 years later from a massive hemorrhage into the opposite hemisphere and pons. No aneurysm was found in any of the cases.

Summary

A follow-up of patients surviving operation for spontaneous progressing intracerebral hemorrhage shows 50% of those with hemorrhage into the temporal lobe still alive with minimal deficit 9 to 13 years following surgery.

Twenty per cent with hemorrhage into the internal capsule are still alive 10 to 12 years following surgery. Some are active with partial hemiparesis and ambulate with foot brace.

Prompt neurosurgical intervention for progressing intracerebral hemorrhage will save lives.

REFERENCES

1. Scott, M.: Cerebral Apoplexy due to Spontaneous Intracranial Hemorrhage. J.A.M.A. **149:** 129–136, 1952.
2. Scott, M.: Neurosurgical Treatment of Spontaneous Intracranial Hemorrhage. J.A.M.A. **172:** 889–895, 1960.

List of College Lectures, 1960

6 January 1960

TILLETT, WILLIAM S. The Use of Enzymes for Therapy. (Nathan Lewis Hatfield Lecture XLIV; *Transactions & Studies*, July 1960).

3 February 1960

STEINER, PAUL E. The Etiology of Human Liver Cancer in Africa and the United States of America. (Thomas Dent Mütter Lecture LXXII; *Transactions & Studies*, October 1960).

2 March 1960

ENDERS, JOHN F. A Consideration of the Mechanisms of Resistance of Viral Infection Based on Recent Studies of the Agents of Measles and Poliomyelitis. (James M. Anders Lecture XXXIX; *Transactions & Studies*, October 1960).

6 April 1960

MIRSKY, I. ARTHUR. Diabetes Mellitus—Past, Present and Future. (Mary Scott Newbold Lecture LXXIX).

19 April 1960

MILLER, GENEVIEVE. The Unicorn in Medical History. (Kate Hurd Mead Lecture XII; *Transactions & Studies*, October 1960).

11 May 1960

Joint Meeting of the Philadelphia County Medical Society and the College of Physicians of Philadelphia.

I. Presentation of the 37th Annual Strittmatter Award of the Philadelphia County Medical Society to Dr. Truman G. Schnabel by Dr. Francis C. Wood, Chairman of the Award Committee.

II. Presentation of the Benjamin Rush Awards for the year 1960 to Mrs. Thomas F. Gates and the Pennsylvania Association of First Aid and Rescue Squads. Presentation by Dr. David A. Cooper, President, Philadelphia County Medical Society.

III. Presentation of citations to physicians who have completed fifty years in the practice of medicine. Citations awarded by Dr. Allen W. Cowley, Sr., President, Medical Society of Pennsylvania.

5 October 1960

MAYERSON, H. S. Observations and Reflections on the Lymphatic System. (Mary Scott Newbold Lecture LXXX; *Transactions & Studies*, January 1961).

2 November 1960

MERRILL, JOHN P. Transplantation of Tissues. (Alvarenga Prize Lecture XX; *Transactions & Studies*, July 1961).

7 December 1960

* WILKINS, ROBERT M. Abnormalities of Sex Differentiation: Classification, Diagnosis, and Treatment. (Thomas Dent Mütter Lecture LXXIII).

13 December 1960

SODEMAN, WILLIAM A. Africa Today—Health and Environmental Influences. (Arthur Parker Hitchens Lecture V; *Transactions & Studies*, July 1961).

* Owing to Dr. Wilkins' illness, this Mütter Lecture was delivered by Robert M. Blizzard, M.D.

Officers, Committees, Sections, and Administrative Staff of the College 1961

President

Thomas M. Durant

Vice-President

John H. Gibbon, Jr.

Secretary

Thomas E. Machella

Treasurer

Jacob H. Vastine, 2nd

Censors

Edward B. Krumbhaar
T. Grier Miller

Honorary Librarian

Richard A. Kern

Truman G. Schnabel
Lewis C. Scheffey

Ex-Presidential Councillors

O. H. Perry Pepper
J. Parsons Schaeffer
Jonathan E. Rhoads

Elective Councillors

To serve until January, 1962
Robert M. Bucher
L. Kraeer Ferguson

To serve until January, 1963
Hugh Montgomery
Allan P. Parker

To serve until January, 1964
Merle M. Miller
John C. Williams

Council

The forenamed and the chairmen of the Standing Committees*

ELECTIVE STANDING COMMITTEES

Library

John Franklin Huber, ch'n
Katharine R. Boucot
George E. Farrar, Jr.
Paul J. Grotzinger
Samuel X Radbill

Hall

Robert F. Norris, ch'n
W. Wallace Dyer
D. Dwight Grove
Charles R. Shuman
George Willauer

Mütter Museum and College Collections

A. Reynolds Crane, ch'n
Henry Brody
Abraham Cantarow

Publications

John M. Howard, ch'n
Fred B. Rogers
Max M. Strumia

* The President is an *ex officio* member of all the Standing Committees.

APPOINTIVE STANDING COMMITTEES

Finance

W. Emory Burnett, ch'n
Richard A. Kern
T. Grier Miller
The Treasurer, *ex officio*

Entertainments

I. S. Ravdin, ch'n
Henry L. Bockus
Thomas Fitz-Hugh, Jr.

Scientific Business

William A. Sodeman, ch'n
Ernest E. Aegerter
A. Reynolds Crane
J. Montgomery Deaver
Francis C. Grant
John M. Howard
Brooke Roberts
Fred B. Rogers
Truman G. Schnabel, Jr.
Kenneth M. Schreck
Isaac Starr
William A. Steiger
Jacob Zatuchni
The Secretary, *ex officio*

Public Health, Preventive Medicine and Public Relations

William A. Steiger, ch'n
Anna-Marie Chirico
Harold L. Hyman
Norman R. Ingraham, Jr.
Tom F. Whayne

SPECIAL COMMITTEES

Weir Mitchell Associates

George I. Blumstein, ch'n
Jonathan E. Rhoads, honorary ch'n

Committee on Bequests

Lewis C. Scheffey, ch'n
Harold L. Goldburgh
Richard A. Kern
William U. McClenahan
Eugene P. Pendergrass
Damon B. Pfeiffer
George Willauer

PRIZE COMMITTEES AND TRUSTEES

Alvarenga Prize and Lectureship

Brooke Roberts, ch'n
Paul J. Grotzinger
Philip J. Hodes
Gulden Mackmull
Robert Robbins

Nathan Lewis Hatfield Prize and Lectureship

Isaac Starr, ch'n
Francis C. Grant
Hubert A. Royster

Weir Mitchell Oration

Francis C. Grant, ch'n
Theodore L. Dehne
Axel K. Olsen
A. M. Ornsteen
Charles Rupp
The President and the Chairman of the Committee on Scientific Business, *ex officio*

Mary Scott Newbold Lectures

John M. Howard, ch'n
Ralph W. Mays
Francis C. Wood
The President and the Chairman of the Committee on Scientific Business, *ex officio*

Trustee under the Will of Thomas Skelton Harrison

J. Parsons Schaeffer

Trustees of Nathan Lewis Hatfield Prize and Lectureship

J. Montgomery Deaver
Thomas Fitz-Hugh, Jr.
H. Curtis Wood, Jr.

Honorary Director of the Department of Medical Art

Samuel B. Sturgis

Honorary Legal Counsel

Eric A. McCouch, Esq.

OFFICERS OF THE SECTIONS

General Medicine

Truman G. Schnabel, Jr., ch'n
Charles R. Shuman, clerk
Executive Committee: Charles M. Thompson, Perry S. MacNeal, Charles J. Schreader

Medical History

Robert J. Gill, ch'n
James F. Toole, clerk
Executive Committee: Nicholas Padis, Fred B. Rogers, Herbert J. Dietrich, Jr.

Ophthalmology

James S. Shipman, ch'n
Thomas H. Cowan, clerk
Executive Committee: Edmund B. Spaeth, Isaac S. Tassman, Harold G. Scheie

Otolaryngology

George L. Whelan, ch'n
William J. Hitschler, clerk
Executive Committee: Douglas Macfarlan, Oram R. Kline, Philip A. Marden

Public Health, Preventive and Industrial Medicine

William A. Steiger, ch'n
Anna-Marie Chirico, clerk
Executive Committee: Lauritz S. Ylvisaker, John J. Hanlon, Fred B. Rogers

ADMINISTRATIVE STAFF OF THE COLLEGE

Librarian
ELLIOTT H. MORSE

Clerk of the College
OLGA E. LANG

Curator, Library Historical Collections
W. B. MCDANIEL, 2d

Editor, Transactions & Studies
FRED B. ROGERS

Curator, Mütter Museum; Custodian, College Collections
ELLA N. WADE

Superintendent
GEORGE S. ALLEN

Fellows

February 15, 1961

ELECTED

1952. Abelson, Neva Martin, 32 Woodale Rd. (18)
1961. Adamson, William C., The Woods Schools, Langhorne, Pa.
1926. Adler, Francis Heed, 313 S. 17th St. (3)
1959. Adlin, Albert, 1512 Lindley Ave. (41)
1949. Aegerter, Ernest E., 3400 N. Broad St. (40)
1953. Agerty, Horst A., 1111 N. 63rd St. (31)
1960. Ainsworth, Thomas H., Jr., 888 Glenbrook Ave., Bryn Mawr, Pa.
1936. Alexander, Fay Knight, Germantown Professional Bldg., Greene and Coulter Sts. (44)
1958. Alexander, John Deaver, Phila. General Hospital (4)
1932. Allen, Frederick H., 3915 Henry Ave. (29)
1953. Allman, David B., 104 St. Charles Pl., Atlantic City, N. J.
1935. Alpers, Bernard J., 111 North 49th St. (39)
1961. Amsterdam, Gerald H., 1351 W. Tabor Rd. (41)
1930. Appel, Kenneth E., 111 N. 49th St. (39)
1905. Appleman, Leighton Francis, 308 S. 16th St. (2)
1960. Arey, James B., 2600 N. Lawrence St. (33)
1959. Arkless, Henry A., 255 S. 17th St. (3)
1935. Armitage, George L., 400 E. 13th St., Chester, Pa.
1922. Arnett, John H., 2116 Pine St. (3)
1952. Ash, Rachel, 255 S. 17th St. (3)
1952. Aston, Melville J., 2507 S. 21st St. (45)
1944. Atkins, Joseph P., 1201 Knox Rd., Wynnewood, Pa.
1956. Atkinson, John B., Chestnut & Copley Rds., Upper Darby, Pa.
1935. Atlee, John L., Jr., 37 E. Orange St., Lancaster, Pa.
1952. Atlee, William A., 37 E. Orange St., Lancaster, Pa.
1958. Ayella, Alfred S., Jr., 1213 S. Broad St. (47)
1935. Bach, Theodore F., 1900 Rittenhouse Sq. (3)
1942. Bachman, Carl, Univ. of Pa. Hospital (4)
1960. Bacon, Catherine L., 504 Howe Rd., Merion Station, Pa.
1937. Bacon, Emily P., Lankenau Medical Bldg. (51)
1960. Bacon, Harry E., 255 S. 17th St. (3)
1958. Baer, Samuel, 5123 N. Broad St. (41)
1959. Baird, Henry Welles, III, 2600 N. Lawrence St. (33)
1952. Baier, Howard N., 3401 N. Broad St. (40)
1952. Baker, Howard W., 3401 N. Broad St. (40)
1946. Baker, Walter W., 255 S. 17th St. (3)
1958. Ball, Simon, 255 S. 17th St. (3)
1958. Ballinger, Walter F., II, 1025 Walnut St. (7)
1957. Baltzell, William Hewson, 1530 Locust St. (2)
1940. Barba, Philip S., 120 Erdenheim Road (18)
1943. Barden, Robert P., 8835 Germantown Ave. (18)
1961. Bare, Wesley W., 2400 S. 21st St. (45)
1939. Barnshaw, Harold D., 526 Cooper St., Camden 2, N. J.
1957. Barr, S. Stanley, 255 S. 17th St. (3)
1939. Bartle, Harvey, Jr., 133 S. 36th St. (4)
1932. Batson, Oscar V., 203 DeKalb Sq. (4)

1921. Bauer, Edward L., Alden Park Manor (44)
1933. Bauer, John T., 312 E. Second St., Moorestown, N. J.
1939. Baumann, Frieda, R.D. 2, West Chester, Pa.
1930. Beardwood, Joseph T., Jr., 2031 Locust St. (3)
1955. Beckfield, William J., Philadelphia General Hospital, 34th & Curie Ave. (4)
1952. Bedrossian, E. Howard, 2027 Spruce St. (3)
1949. Beecham, Clayton T., 105 West School Lane (44)
1935. Beerman, Herman, 255 S. 17th St. (3)
1942. Behrend, Albert, 1018 Melrose Ave. (26)
1945. Behrend, Bernard, 5910 Greene St. (44)
1934. Behrend, Moses, Rittenhouse Claridge, 18th & Walnut St. (3)
1949. Beizer, Lawrence H., 304 S. 19th St. (3)
1930. Belk, William Parks, 433 Owen Rd., Wynnewood, Pa.
1936. Bell, Benjamin Tertius, 1941 Woodland Rd., Abington, Pa.
1956. Beller, Martin Leonard, 1936 Spruce St. (3)
1947. Bellet, Samuel, 2021 Spruce St. (3)
1956. Belmont, Owen, 5723 No. Park Ave. (41)
1959. Berk, Nathaniel G., 2534 W. Cheltenham Ave. (50)
1941. Bernstein, Mitchell, 2053 S. John Russell Circle (17)
1951. Bernstine, J. Bernard, 255 S. 17th St. (3)
1960. Bernstine, Melvin Lewis, 1543 Marmont Lane, Los Angeles 46, Cal.
1956. Berry, Theodore J., 331 E. Lancaster Ave., Wynnewood, Pa.
1957. Biele, Albert M., 1530 Locust St. (2)
1918. Billings, Arthur E., 2020 Spruce St. (3)
1952. Bird, Gustavus C., Jr., 3401 N. Broad St. (40)
1957. Birdsall, Thomas M., 255 S. 17th St. (3)
1949. Bishop, Edward H., 811 Spruce St. (7)
1933. Bishop, Paul A., Pennsylvania Hospital, (7)
1944. Blady, John V., Parkway House, 2201 Benjamin Franklin Pkwy. (30)
1960. Blake, Alton D., Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Blake, Paul O., 273 N. Lansdowne Ave., Lansdowne, Pa.
1958. Blakemore, William S., 3400 Spruce St. (4)
1917. Block, Frank B., A1124 Park Drive Manor (44)
1957. Block, Louis H., 1351 Tabor Rd. (41)
1949. Blumstein, George I., 2039 Delancey St. (3)
1929. Bockus, Henry L., 250 S. 18th St. (3)
1928. Boles, Russell S., Rittenhouse Plaza, 1901 Walnut St. (3)
1923. Bond, Earl D., 111 N. 49th St. (39)
1961. Bongiovanni, Alfred M., 1740 Bainbridge St. (46)
1948. Bookhammer, Robert S., 209 Rittenhouse Claridge (3)
1931. Bortz, Edward Le Roy, 2021 W. Girard Ave. (30)
1936. Bostwick, Delazon Swift, 106 Linwood Ave., Ardmore, Pa.
1928. Bothe, Frederick A. Wynnewood Plaza, Wynnewood, Pa.
1951. Boucot, Katharine R., 3300 Henry Ave. (29)
1947. Bourland, Henry S., 2219 Garret Rd., Drexel Hill, Pa.
1954. Bowers, Paul A., 2035 Locust St. (3)
1942. Bowie, Morris A., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1907. Bradley, William Nathaniel, 2414 Knowles Rd., Graylyn Crest, Wilmington 3, Del.
1959. Brady, Luther Weldon, Jr., Hahnemann Hospital, Broad & Race Sts. (2)
1954. Bralow, S. Philip, 3701 N. Broad St. (40)
1942. Branen, William, T., Whitby & Cypress Aves., Yeadon, Pa.
1921. Bransfield, John W., 2031 Locust St. (3)

1948. Braun, William, 406 Cooper St., Camden, N. J.
1953. Brav, Solomon S., 5575 N. Park Ave. (41)
1953. Breckenridge, Robert L., Our Lady of Lourdes Hosp., 1600 Haddon Ave., Camden 3, N. J.
1961. Breslow, Irwin H., 419 S. 19th St. (46)
1946. Briscoe, Clarence Conway, 811 Spruce St. (7)
1953. Brobeck, John R., Univ. of Pa. School of Medicine (4)
1958. Brody, Henry, Einstein Medical Center, York & Tabor Rds. (41)
1952. Brody, Morris W., 1930 Chestnut St. (3)
1948. Brogan, Edmund J., Thomas Wynne Apartment, Wynnewood, Pa.
1953. Brooke, John A., 1431 Spruce St. (2)
1958. Brooks, Frank P., Hospital of the Univ. of Pa. (4)
1936. Brown, Clark E., Lancaster Ave. & City Line Ave. (51)
1932. Brown, Claude P., 1930 Chestnut St. (3)
1959. Browneller, Ellsworth R., Jefferson Hospital (7)
1961. Brunt, Manly Y., 111 N. 49th St. (39)
1939. Brust, Raymond, M., 4710 Chester Ave. (43)
1953. Bucher, Robert M., 3401 N. Broad St. (40)
1961. Buerk, Minerva S., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Bumgardner, Heath D., 3701 N. Broad St. (40)
1940. Burnett, W. Emory, 3401 N. Broad St. (40)
1954. Burros, Harry M., 419 S. 19th St. (46)
1941. Butler, Miriam, Watersmeet, Glen Mills, Pa.
1957. Calhoun, John Alfred, Jr., 214 Elm Ave., Swarthmore, Pa.
1958. Cameron, Charles S., 235 N. 15th St. (2)
1928. Campbell, Edward H., 133 S. 36th St. (4)
1952. Campbell, Edward W., Abington Memorial Hospital
1944. Campion, Richard J., Box 136 Springhouse, Ambler, Pa.
1960. Cancelmo, John B., 5012 Spruce St. (39)
1931. Cantarow, Abraham, 1025 Walnut St. (7)
1952. Cardone, John B., 831 N. 63rd St. (31)
1935. Carey, Lawrence S., 330 S. 9th St. (7)
1931. Cariss, Walter L., 51 N. 39th St. (4)
1956. Carnwath, John Wallace, Summit & Highland Aves., Jenkintown, Pa.
1930. Carpenter, Chapin, 1930 Chestnut St. (3)
1959. Carrington, Elsie R., 3401 N. Broad St. (40)
1960. Carroll, Robert T., 1015 Sansom St. (7)
1917. Carson, John B., Newton Square, Pa.
1956. Carty, James Byron, 51 Hampden Rd., Upper Darby, Pa.
1956. Casey, Paul R., 8350 Roosevelt Blvd. (15)
1937. Castallo, Mario A., 1621 Spruce St. (3)
1943. Castigliano, S. Gordon, 853 Mt. Pleasant Rd., Bryn Mawr, Pa.
1949. Caswell, H. Taylor, 3401 N. Broad St. (40)
1954. Catenacci, Alfred J., 1417 S. Broad St. (47)
1954. Cathcart, Richard T., 739 S. Broad St. (47)
1957. Cattie, Vincent J., The Benson, E. 207A., Jenkintown, Pa.
1950. Chamberlain, Richard H., 3400 Spruce St. (4)
1939. Chamberlin, George W., Reading Hospital, Reading, Pa.
1900. Chance, Burton, 9 Llanalew Road, Haverford, Pa.
1945. Chance, Burton, Jr., 8236 Germantown Ave. (18)
1958. Channick, Bertram J., 3701 N. Broad St. (40)
1954. Charny, Charles W., 2039 Delancey Pl. (3)
1960. Chirico, Anna-Marie, Hosp. of Univ. of Pa. (4)

1947. Chouké, Keihar S., P. O. Box 447, Kecoughton, Va.
1945. Cianfrani, Theodore, 1930 Chestnut St. (3)
1939. Ciccone, Emmet F., 2021 Murray St. (15)
1960. Cinquino, Mario A., 1518 S. Broad St. (46)
1960. Clader, Stanley C., 825-A Glenbrook Ave., Bryn Mawr, Pa.
1951. Clagett, Augustus H., Jr., 1618 N. Broom St., Wilmington 6, Del.
1929. Clark, Eliot R., 315 S. 41st St. (4)
1951. Clark, John K., 36th & Spruce Sts. (4)
1947. Clark, Thomas Williams, 218 W. Chestnut Hill Ave.
1947. Classen, Charles H., Cushman Rd. and Lancaster Ave., Rosemont, Pa.
1958. Closson, Edward W., 2320 S. Broad St. (45)
1910. Cloud, J. Howard, 111 St. Pauls Road, Ardmore, Pa.
1957. Cohen, Frank L., 2113 Spruce St. (3)
1949. Cohen, Louis B., 1320 Arrott St. (24)
1953. Cohen, Robert V., 520 Spring Ave., Elkins Park 17, Pa.
1934. Collins, Leon Howard, Jr., 133 S. 35th St. (4)
1943. Colonna, Paul C., 133 S. 36th St. (4)
1949. Conger, Kyril B., 3401 N. Broad St. (40)
1961. Coon, Julius M., 1025 Walnut St. (7)
1945. Coonel, Pauline, 47 E. Mt. Pleasant Ave. (19)
1930. Cooper, David A., 1520 Spruce St. (2)
1953. Cooper, Donald R., Woman's Medical College, 3300 Henry Ave. (29)
1960. Cooper, Edward Sawyer, 6710 Lincoln Drive (19)
1947. Coppolino, John F., 1807 S. Broad St. (45)
1952. Corbit, John D., Jr., 3717 Chestnut St. (4)
1959. Cormeny, George F., 3818 Chestnut St. (4)
1941. Cornelius, Chalmers E., 119 Summit Ave., Jenkintown, Pa.
1911. Cornell, Walter S., Board of Public Education, Parkway and 21st St. (3)
1914. Corson, Edward F., 136 S. 16th St. (2)
1946. Costello, Thomas J. 825 Glenbrook Ave., Bryn Mawr, Pa.
1924. Cowan, Alfred, 1930 Chestnut St. (3)
1940. Cowan, Thomas H., 1930 Chestnut St. (3)
1907. Crampton, George S., 2031 Locust St. (3)
1947. Crane, A. Reynolds, 807 Spruce St. (7)
1937. Crane, Martin P., 4701 Pine St. (43)
1952. Crellin, J. Antrim, 1930 Chestnut St. (3)
1955. Crist, Walter A., 211 N. 5th St., Camden, N. J.
1921. Crossan, Edward T., Buttonwood Hall, Conshohocken, Pa.
1937. Crump, Jean, R. D. 2, West Chester, Pa.
1959. Cullen, Milton L., 1321 W. Tabor Rd. (41)
1934. Custer, R. Philip, 643 Moreno Road, Narberth, Pa.
1958. D'Alonzo, Walter A., 1647 S. 15th St. (45)
1938. Dannenberg, Arthur M., Sr., 235 S. 15th St. (2)
1950. Dannenberg, Arthur M., Jr., Henry Phipps Institute, Univ. of Pa. (4)
1951. Daugherty, Earl A., 2025 W. Girard Ave. (30)
1953. Davie, John H., 37 S. 20th St. (3)
1947. Davis, C. Nelson, 133 South 36th St. (4)
1936. Davis, David M., 255 S. 17th St. (3)
1957. Davis, John Evan, Tedwyn Apts., 840 Montgomery Ave., Bryn Mawr, Pa.
1951. Davis, J. Wallace, 135 S. 18th St. (3)
1937. Davis, Perk Lee, P. O. Box 701, Paoli, Pa.
1961. Dawber, Bryan A., Penn Mutual Life Insurance Co. (5)

1935. Deaver, J. Montgomery, Lankenau Medical Bldg. (51)
1957. Decker, John Paul, Pennsylvania Hospital (7)
1957. Dees-Porch, Frances, Glendale Road & Chestnut Sts., Upper Darby, Pa.
1947. Dehne, Theodore L., Adams Avenue and Roosevelt Blvd. (24)
1935. Deibert, Irvin Elmer, 538 Cooper St., Camden, N. J.
1958. Deitz, George W. III, 1146 Arrott St. (24)
1923. De Long, Perce, Presidential Apts. (31)
1955. De Long, Samuel L., 860 Lancaster Ave., Bryn Mawr, Pa.
1952. DeLuca, Charles Q., 255 S. 17th St. (3)
1952. De Orsay, Ralph H., 1241 Lindale Ave., Drexel Hill, Pa.
1951. De Palma, Anthony F., 248 S. 21st St. (3)
1959. DeTuerk, John J., 1930 Chestnut St. (3)
1928. Dewees, A. Lovett, Glen Mills, Del. Co., Pa.
1959. Dickens, Helen O., 1512 W. Oxford St. (21)
1958. Dickstein, Benjamin, 6810 Castor (24)
1956. Dietrich, Herbert James, Jr., 1830 Delancey Place (3)
1952. Diglio, Victor A., 2200 St. James Place (17)
1960. Dinon, Louis R., 330 S. 9th St. (7)
1920. Doane, Joseph C., 617 W. Hortter St. (19)
1948. Dohan, Francis Curtis, 80 Princeton Road, Cynwyd, Pa.
1954. Donaldson, James B., 1901 Walnut St. (3)
1946. Donnelly, Andrew J., 33rd and Powelton Ave. (4)
1933. Donnelly, Joseph C., 6832 Ogontz Ave. (38)
1937. Donnelly, Robert T. M., 5205 N. Broad St. (41)
1954. Downing, Daniel F., 8864 Norwood Ave. (18)
1952. Drayer, Calvin S., 111 N. 49th St. (39)
1949. Dripps, Robert D., 3400 Spruce St. (4)
1935. Duane, William, Jr., 2109 Spruce St. (3)
1956. Dubin, Isadore N., Woman's Medical College (29)
1944. Dublin, George J., 1930 Chestnut St. (3)
1944. Dugger, John H., Episcopal Hospital (25)
1935. Duncan, Garfield G., 330 S. 9th St. (7)
1951. Dunne, Francis S., 133 S. 36th St. (4)
1953. Dupler, Donald A., 4028 Walnut St. (4)
1942. Durant, Thomas M., 3401 N. Broad St. (40)
1947. Durkin, John Keenan, 49 Woodcroft Rd., Havertown, Pa.
1942. Dyer, W. Wallace, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1935. Eads, John T., 607 E. Durham St. (19)
1936. Easby, Mary Hoskins, R. D. 1, Burlington, Vt.
1948. Eaton, Francis H., 4007 Chestnut St. (39)
1937. Edeiken, Joseph, 2130 Delancey Pl. (3)
1944. Eger, Sherman A., 255 S. 17th St. (3)
1944. Ehrich, William E., 540 W. Hortter St. (19)
1956. Eiman, John W., Abington Memorial Hospital, Abington, Pa.
1959. Eisenhower, James S. D., Jr., 2704 Pacific Ave., Wildwood, N. J.
1958. Eisman, Sylvan H., 3600 Spruce St. (4)
1946. Elfman, Louis Kenneth, 6330 Lebanon Avenue (31)
1959. Elias, Elmer J., 474 Greenwood Ave., Trenton, N. J.
1949. Elkinton, J. Russell, Oak Lane, Moylan, Pa.
1957. Ellis, Richard A., 1711 Rittenhouse Square (3)
1955. Ellis, Samuel, 541 S. 46th St. (43)
1939. Ellis, Van Mashburn, 1528 Spruce St. (2)

1928. Ellison, Richard T., 8601 Stenton Ave. (18)
1936. Ellson, J. Vernon, Glendale Road & Chestnut St., Upper Darby, Pa.
1937. Elsom, Kendall A., Maloney Clinic Bldg., 36th & Spruce Sts. (4)
1934. Ely, William C., 3912 Chestnut St. (4)
1932. Engel, Gilson C., Lankenau Medical Bldg. (51)
1945. English, O. Spurgeon, 3401 N. Broad St. (40)
1942. Erb, William H., 133 S. 36th St. (4)
1957. Erdman, William James, II, 3400 Spruce St. (4)
1950. Ersner, Matthew S., 1915 Spruce St. (3)
1957. Etzl, Michael M., 9025 Frankford Ave. (14)
1954. Evans, William W., Box 2, Bryn Mawr, Pa.
1948. Everts, Glenn S., 5515 Wissahickon Ave., Apt. D-403. (44)
1955. Eynon, Harold K., Route 70 at East Gate, Barclay Farm, Haddonfield, N. J.
1946. Farell, David M., 1912 Spruce St. (3)
1903. Farr, Clifford B., Railroad Ave. & County Line Rd., Bryn Mawr, Pa.
1945. Farrar, George Elbert, Jr., 528 Scott Rd., Gladwyne, Pa.
1953. Farrell, Harry L., 1930 Chestnut St. (3)
1930. Farrell, John T., Jr., 255 S. 17th St. (3)
1935. Ferguson, Lewis Kraeer, 419 S. 19th St. (46)
1936. Fetter, Ferdinand, 322 S. 21st St. (3)
1945. Fetter, John S., 842 Worrell Rd., Jenkintown, Pa.
1935. Fetter, Theodore R., 255 S. 17th St. (3)
1924. Fewell, Alexander G., 1924 Pine St. (3)
1952. Fields, Harry, 133 S. 36th St. (4)
1959. Fineberg, Charles, 255 S. 17th St. (3)
1955. Finestone, Albert J., 2039 Pine St. (3)
1960. Finkbiner, Rodman B., 811 Spruce St. (7)
1943. Finkelstein, Arthur, 480 Latch's Lane, Merion, Pa.
1955. Finkelstein, David, 419 S. 19th St. (46)
1955. Finley, John K., 527 Welsh St., Chester, Pa.
1954. Finn, Joseph L., 8014 Burholme Ave., (11)
1947. First, Arthur, 1714 Spruce St. (3)
1960. First, Howard E., 1714 Spruce St. (3)
1954. Fischer, Carl C., Girard College (21)
1950. Fischer, H. Keith, 100 W. Coulter St. (44)
1958. Fisher, Robert M., 118 Airdale Rd., Rosemont, Pa.
1956. Fite, Franklin K., Germantown Hospital (44)
1952. Fitts, William T., Jr., 3400 Spruce St. (4)
1928. Fitz-Hugh, Thomas, Jr., 2016 Delancey Pl. (3)
1952. Flexner, Louis B., 248 Anatomy-Chemistry Bldg., Univ. of Pa.
1928. Flick, John B., 819 Black Rock Rd., Gladwyne, Pa.
1954. Flick, John B., Jr., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1952. Flinn, Lewis B., 503 Delaware Ave., Wilmington, Del.
1939. Flippin, Harrison F., Lankenau Hospital (51)
1957. Forman, Simon B., 255 S. 17th St. (3)
1957. Fornwalt, George R., Brandon Road & Ludlow St., Upper Darby, Pa.
1954. Forster, H. Walter, Jr., 37 S. 20th St. (3)
1960. Foulger, John H., 601 Rockwood Rd., Wilmington (2) Del.
1941. Fox, C. Calvin, 1806 Spruce St. (3)
1957. Frankel, Donald S., 255 S. 17th St. (3)
1959. Frankel, Kalman, 111 N. 49th St. (39)
1955. Frayer, William C., 37 S. 20th St. (3)

1941. Frazier, William Doane, 419 Gilpin Rd., Narberth, Pa.
1952. Freed, Herbert, 255 S. 17th St. (3)
1956. Freedman, Joseph T., 8-A Rittenhouse Plaza (3)
1958. Freiwald, Milton J., 1530 Spruce St. (2)
1953. Fried, Paul H., 1812 Spruce St. (3)
1955. Friedenberg, Zachary B., 133 S. 36th St. (4)
1951. Friedman, Paul Sigmund, 1422 Chestnut St. (2)
1960. Friedmann, Sidney, 1740 Bainbridge St. (46)
1958. Frisch, Frederick, 40 Morris Ave., Bryn Mawr, Pa.
1933. Fritch, James Scott, 269 S. 19th St. (3)
1937. Fritz, Herbert H., Pennswood Rd., Bryn Mawr, Pa.
1953. Fruchter, Joseph M., 2200 Benjamin Franklin Parkway, Park Towne, North (30)
1940. Fry, Kenneth E., 1719 Rittenhouse Sq. (3)
1935. Fry, Wilfred Eyles, 1930 Chestnut St. (3)
1937. Furlong, Thomas F., Jr., Times Medical Building, Ardmore, Pa.
1954. Gambescia, Joseph M., 1422 Race St. (2)
1935. Gammon, Geo. D., Univ. of Pa. Hospital (4)
1951. Garlichs, Richard W., 216 N. Manoa Road, Havertown, Pa.
1931. Garner, Vaughn C., Germantown Professional Building (44)
1953. Garnet, James D., 807 Spruce St. (7)
1959. Gartland, John J., 269 S. 19th St. (3)
1950. Garvin, Eugene J., 533 S. 46th St. (43)
1953. Geckeler, Edwin O., 269 S. 19th St. (3)
1952. Gefter, William I., 366 Penn Rd., Wynnewood, Pa.
1935. Geist, Donald C., 1930 Chestnut St. (3)
1955. Gelfand, David, 1722 Pine St. (3)
1954. German, George B., 429 Cooper St., Camden, N. J.
1941. Gershon-Cohen, J., 255 S. 17th St. (3)
1959. Gerson, Irvin M., 1561 E. Tulpehocken St. (38)
1955. Gettes, Bernard C., 128 Overhill Rd., Cynwyd, Pa.
1934. Gibbon, John H., Jr., 1025 Walnut St. (7)
1939. Gibson, Glen Gregory, 2031 Locust St. (3)
1944. Gifford, Edward S., Jr., 1913 Spruce St. (3)
1954. Gilbert, Philip D., Cooper Hospital, Camden, N. J.
1954. Giletto, Basil J., 2020 Locust St. (3)
1920. Gill, A. Bruce, 1603 Normandy Drive, Mt. Dora, Fla.
1956. Gill, Robert J., 801 Spruce St. (7)
1927. Gilmour, William R., 6616 Woodland Ave. (42)
1952. Gilpin, Sherman F., Jr., 1023 Buery Building, 3701 N. Broad St.
1949. Ginsburg, Isadore W., 3401 N. Broad St. (40)
1931. Giordano, Anthony A. S., 129 West Carpenter Lane (19)
1958. Girsh, Leonard S., 3701 N. Broad St. (40)
1954. Gislason, Gerhard J., 136 S. 16th St. (2)
1956. Goldberg, Harry, 7913 Rolling Green Rd., Cheltenham, Pa.
1933. Goldburgh, Harold L., 1932 Spruce St. (3)
1958. Golub, Leib J., 136 S. 16th St. (2)
1949. Gopadze, Illarion I., 255 S. 17th St. (3)
1956. Goracci, Armando F., 2040 Poplar St. (30)
1937. Gordon, William, 5345 Spruce St. (39)
1956. Gouley, Benjamin, 5577 N. Park Ave. (41)
1957. Grahn, Henry Victor, 5132 Chester Ave. (43)
1926. Grant, Francis Clark, 750 Germantown Pike, Lafayette Hill, Pa.

1958. Greco, Toby A., 2506 S. 20th St. (45)
1940. Greene, Lloyd B., 803 Spruce St. (7)
1952. Greening, Roy R., Dept. of Radiology, Jefferson Hospital (7)
1958. Greenspan, Benjamin, 1319 W. Tabor Rd. (41)
1955. Greenstein, Raphael H., 1710 Pine St. (3)
1934. Griffith, John Q., Jr., 6 N. Fredericksburg Ave., Margate, N. J.
1945. Griffiths, John E., Mermont Apartments, Bryn Mawr, Pa.
1941. Groff, Robert A., Univ. of Pa. Hospital (4)
1952. Grotzinger, Paul J., 2121 Valley Rd., Huntingdon Valley, Pa.
1952. Grove, D. Dwight, 230 N. Broad St. (2)
1945. György, Paul, Univ. of Pa. School of Medicine (4)
1935. Hadden, Samuel B., 250 S. 18th St. (3)
1951. Hafkenschiel, Joseph H., Jr., 302 Lankenau Medical Bldg. (51)
1945. Hahn, George A., 255 S. 17th St. (3)
1935. Haines, Harlan F., 134 S. State Rd., Upper Darby, Pa.
1955. Hallahan, John D., 104 W. Front St., Media, Pa.
1951. Hallett, Joseph W., 136 S. 16th St. (2)
1961. Hammett, Van Buren O., 111 N. 49th St. (39)
1959. Hampton, Louis J., 1025 Walnut St. (7)
1954. Hand, B. Marvin, 210 N. 15th St. (2)
1938. Hand, John G., 1724 Pine St. (3)
1947. Hanes, William James, 218 E. Beechtree Lane, Wayne, Pa.
1958. Hanlon, John J., 519 City Hall Annex (7)
1950. Hansen, A. Victor, 3401 N. Broad St. (40)
1957. Harasym, Emil L., 952 N. Franklin St. (23)
1956. Harbert, Frederick, Jefferson Hospital (7)
1952. Harer, W. Benson, State Rd. & Rogers Ave., Bywood, Pa.
1951. Harkins, Herbert P., 1930 Chestnut St. (3)
1959. Harris, James S. C., 5401 Wayne Ave. (44)
1932. Harris, Stanley E., 229 Maple Ave., Delanco, N. J.
1948. Harris, T. N., 5112 Woodbine Ave. (31)
1929. Harrison, Francis G., 1900 Spruce St. (3)
1926. Hartmann, Fred I., 1914 Pine St. (3)
1946. Harvey, Edith E., 406 York Rd., Jenkintown, Pa.
1947. Harvey, Rolfe Marsh, 669 Mill Rd., Villanova, Pa.
1961. Harvie, Fred H., 3400 Spruce St. (4)
1935. Haskell, Benjamin F., 1427 Spruce St. (2)
1958. Haupt, George J., 1012 Walnut St. (7)
1960. Hausman, David H., Pennsylvania Hospital, 8th & Spruce Sts. (7)
1947. Havens, Walter Paul, Jr., 139 Cheswold Lane, Haverford, Pa.
1947. Hawthorne, Herbert Reid, 419 S. 19th St. (46)
1952. Hayllar, Benjamin L., 803 Spruce St. (7)
1961. Hayward, Malcolm L., 111 N. 49th St. (39)
1957. Hedges, Thomas R., Jr., 1711 Rittenhouse St. (3)
1946. Hendrickson, Frank O., 140 N. Rolling Rd., Springfield, Pa.
1953. Henny, George C., 3400 N. Broad St. (40)
1944. Herbut, Peter A., Dept. of Pathology, Jefferson Medical College Hospital (7)
1954. Herron, James R., 1486 Haddon Ave., Camden 3, N. J.
1957. Hess, Catherine B., 338 Gowan Ave. (19)
1949. Heyl, W. Meredith, 100 W. Coulter St. (44)
1956. Hildreth, Eugene A., University of Penna. Hospital (4)
1952. Hinkson, DeHaven, 329 N. 40th St. (4)

1924. Hirst, John C., 2d., 500 N. 20th St. (30)
1943. Hitschler, William J., Bethlehem Pike & Summit (18)
1944. Hneleski, Ignatius S., 802 S. 48th St. (43)
1943. Hockaday, Agnes, 316 Shadeland Ave., Drexel Hill, Pa.
1939. Hodes, Philip J., Dept. of Radiology, Jefferson Medical College (7)
1947. Hodges, John H., 1025 Walnut St. (7)
1959. Hoffman, Francis H., 3401 N. Broad St. (40)
1948. Hoffman, George L., Jr., 133 S. 36th St. (4)
1954. Hollander, George, 3500 Vista St. (36)
1949. Hollander, Joseph L., 36th & Spruce Sts. (4)
1951. Hollis, Charles B., 28 W. School Lane (44)
1952. Holloway, Edward E., 1736 Pine St. (3)
1949. Hopkins, Henry U., Garden Court Apts., 47th & Pine Sts. (43)
1953. Horan, Charles A., 734 N. 63rd St. (31)
1946. Horan, Gerald W., 5819 Chester Ave. (43)
1947. Horwitz, Orville, Hospital of University of Pa. (4)
1950. Houlihan, Carl T., 207 McClatchy Bldg., Upper Darby, Pa.
1944. Houlsel, Edmund L., 255 S. 17th St. (3)
1928. Houser, Karl Musser, 2035 Delancey Pl. (3)
1958. Howard, John M., 230 N. Broad St. (2)
1948. Howland, Alvin Wilcox, 255 S. 17th St. (3)
1946. Howson, John Yeatts, 316 Lancaster Ave., Wayne, Pa.
1951. Hubbard, John P., University of Penna. School of Medicine (4)
1947. Huber, John Franklin, Temple University School of Medicine (40)
1937. Hughes, Joseph, 111 N. 49th St. (39)
1939. Hughes, P. Boland, 419 Hillbrook Rd., Bryn Mawr, Pa.
1951. Hundley, J. Warren, 3818 Chestnut St. (4)
1954. Hunsicker, William C., Jr., 255 S. 17th St. (3)
1946. Hunt, William T., Jr., 6 Penn Center Plaza (3)
1921. Hunter, Robert John, 928 N. 63rd St. (31)
1952. Hyman, Harold L., 3401 N. Broad St. (40)
1950. Imbriglia, Joseph E., 329 Shadeland Ave., Drexel Hill, Pa.
1952. Imperiale, C. Charles, 1331 Pine St. (7)
1949. Ingraham, Norman R., Jr., Stenton and Whitemarsh Aves., (18)
1957. Isaacson, Howard, Haverford Ave. & Drexel Rd.
1951. Isard, Harold J., Mt. Sinai Hospital, 5th & Reed Sts. (47)
1951. Israel, Harold L., 304 S. 19th St. (3)
1947. Israel, S. Leon, 2116 Spruce St. (3)
1952. Iverson, Preston C., 1930 Chestnut St. (3)
1947. Jaeger, Rudolph, Jefferson Medical College Hospital (7)
1952. Janton, O. Henry, 2008 Walnut St. (3)
1941. Jeffers, William A., 503 Owen Road, Wynnewood, Pa.
1960. Jenson, William K., 330 S. 9th St. (7)
1943. Johnson, Julian, 3400 Spruce St. (4)
1959. Johnson, Robert G., 1012 Walnut St. (7)
1938. Johnson, Thomas A., 135 S. 18th St. (3)
1952. Jonas, Karl C., 2601 Parkway (30)
1957. Jordan, Luke W., 1486 Haddon Ave., Camden 3, N. J.
1957. Kacher, Leon, 2037 Pine St. (3)
1936. Kain, Thomas M., 403 Cooper St., Camden, N. J.
1957. Kane, Sydney H., 3458 Cottman Ave. (49)
1948. Kaplan, Louis, 2040 Pine St. (3)

1938. Kasper, Kelvin A., 135 S. 18th St. (3)
1958. Kasser, Max D., 37 S. 20th St. (3)
1945. Katz, G. Henry, 111 N. 49th St. (39)
1958. Katz, Jacob, 136 S. 16th St. (2)
1941. Kauffman, M. Luther, Medical Arts Bldg., Jenkintown, Pa.
1947. Kay, Calvin Frederick, Univ. of Pa. Hospital (4)
1954. Kaye, Robert, Children's Hospital, 1740 Bainbridge St. (46)
1947. Keefer, George Pfahler, 136 S. 16th St. (2)
1949. Keiserman, Joseph, 5460 Baltimore Ave. (43)
1959. Keitel, Hans G., 1025 Walnut St. (7)
1932. Kelly, Herbert T., 1900 Spruce St. (3)
1961. Kelly, William E., 111 N. 49th St. (39)
1941. Kennedy, Patrick J., 32 Hampden Rd., Upper Darby, Pa.
1948. Kern, Franklin Moore, 903 Nicholson Rd., Wynnewood, Pa.
1921. Kern, Richard A., Temple University Hospital, 3401 N. Broad St. (40)
1935. Keyes, Baldwin L., 2031 Locust St. (3)
1960. Kimmich, John M., Campbell Company, Camden, N. J.
1936. King, Orville C., 330 S. 9th St. (7)
1958. Kirby, Charles K., 3400 Spruce St. (4)
1952. Kirshner, Jacob J., 1930 Chestnut St. (3)
1960. Kitchell, J. Roderick, 3719 Chestnut St. (4)
1920. Klauder, Joseph V., 1934 Spruce St. (3)
1920. Klein, Thomas, 250 S. 18th St. (3)
1952. Kleinbart, Morris, 1922 Pine St. (3)
1954. Kligman, Albert M., 36th & Spruce Sts. (4)
1934. Kline, Oram R., 514 Cooper St., Camden, N. J.
1959. Kline, Oram R., Jr., 524 Cooper St., Camden, N. J.
1948. Klingensmith, Paul O., Med. Science Bldg., Lankenau Hosp. (51)
1958. Klingensmith, Walter C., 3600 Spruce St. (4)
1956. Klinghoffer, June F., 5501 Green St. (44)
1932. Klopp, John W., Gwynedd Valley, Pa.
1919. Knipe, Norman L., 602 Washington Lane, Jenkintown, Pa.
1960. Knopf, Carl L., 5312 Spruce St. (39)
1960. Knorr, John K., 3rd., Lankenau Medical Bldg. (51)
1959. Knowles, Harry J., 255 S. 17th St. (3)
1945. Kobler, H. B., 658 N. 63rd St. (31)
1959. Koiwai, Eichi Karl, 235 N. 15th St. (2)
1914. Kolmer, John A., Cynwyd, Pa.
1957. Koltes, John A., Jefferson Hospital, 14th Annex, 10th & Sansom Sts. (7)
1936. Konzelmann, Frank Williamson, Shore Memorial Hosp., Somer's Point, N. J.
1949. Koop, C. Everett, 1740 Bainbridge St. (46)
1952. Kornblueh, Igho H., Welsh Rd., & Verree Rd. (15)
1958. Kovach, Coleman W., 2031 Locust St. (3)
1941. Krall, J. Thomas, 1927 Spruce St. (3)
1948. Kramer, David W., 2007 Pine St. (3)
1954. Krasnoff, Sidney O., Tabor Medical Bldg., York & Tabor Roads (41)
1944. Krauss, Frederick Harold, 136 S. 16th St. (2)
1952. Kravitz, Charles H., 626 Ashbourne Rd., Elkins Park, Pa.
1949. Kressler, Robert J., 330 S. 9th St. (7)
1941. Krewsen, William E., 3rd., 1930 Chestnut St. (3)
1914. Krumbhaar, Edward B., P. O. Box 4056 (18)
1947. Kuhlenbeck, Hartwig, Woman's Medical College, 3300 Henry Ave. (29)

1947. La Boccetta, Alfred Charles, Phila. General Hospital, 34th St. & Curie Ave. (4)
1952. Lachman, John W., 3401 N. Broad St. (40)
1949. La Clair, Charles H., Jr., 1021 W. Main St., Norristown, Pa.
1951. Lame, Edwin L., 51 N. 39th St. (4)
1950. Lamont, Austin, 3400 Spruce St. (4)
1946. Lampe, William T., 4207 Tyson Ave. (35)
1952. Lang, Warren R., 1012 Walnut St. (7)
1941. Langner, Paul H., Jr., 1208 Edmonds Ave., Drexel Hill, Pa.
1945. Lansbury, John, 3401 N. Broad St. (40)
1926. Laws, George M., 1907 Spruce St. (3)
1936. Leaman, William G., Jr., Presidential Apts: Adams House B-909. (31)
1950. Learner, Norman, 3701 N. Broad St. (40)
1920. Leavitt, Frederic Headley, 1527 Pine St. (2)
1957. Lee, Charles Trumbull, Jr., 33 E. Chestnut Hill Ave. (18)
1941. Leberman, Paul R., 136 S. 16th St. (2)
1942. Lehman, James A., The Stafford House, Chelten & Wissahickon Ave. (44)
1952. Lehman, J. Stauffer, 230 N. Broad St. (2)
1961. Leibfried, Jane M., 5501 Greene St. (44)
1960. Leiter, Samuel S., 1301 Westbury Drive, Overbrook Park (31)
1951. Leivy, Frank E., 255 S. 17th St. (3)
1944. Lell, William A., 333 S. 18th St. (3)
1935. Lemmon, William T., 133 S. 36th St. (4)
1943. Leopold, Irving H., 1711 Rittenhouse Sq. (3)
1955. Leopold, Robert L., 269 S. 19th St. (3)
1944. Lettiere, Anthony J., 425 E. State St., Trenton, N. J.
1933. Levering, J. Walter, Abington Memorial Hospital, Abington, Pa.
1959. Levick, Leonard J., 1300 E. Cliveden St. (19)
1958. Levine, Samuel, 7100 N. 19th St. (38)
1958. LeWinn, Edward B., 1351 Devereaux Ave. (11)
1960. Lewis, David H., Philadelphia General Hosp. (4)
1915. Lewis, Fielding O., Providence Road, Media, Pa.
1960. Lewis, George C., Jr., 133 S. 36th St. (4)
1938. Lewis, James P., 3815 Chestnut St. (4)
1955. Lieberman, George E., 2019 Pine St. (3)
1956. Likoff, William, 249 N. Broad St. (2)
1940. Limberger, William A., 301 S. Church St., West Chester, Pa.
1958. Lin, David Y. P., 2228 S. Broad St. (45)
1938. Lindauer, M. August, 133 S. 36th St. (4)
1956. Lindquist, John N., 422 Sabine Ave., Wynnewood, Pa.
1927. Lindsey, Walter H., 325 Callowhill St., Perkasie, Pa.
1936. Lintgen, Charles, 1930 Chestnut St. (3)
1958. Lipschutz, Arthur, 7974 Fayette St. (19)
1959. Lipschutz, Herbert, 255 S. 17th St. (3)
1953. Lipsius, Edward I., 319 S. 16th St. (3)
1945. Lisker, Samuel, 255 S. 17th St. (3)
1959. Little, Ralph B., 111 N. 49th St. (39)
1944. Livezey, Mary M., 7200 Cresheim Rd. (19)
1936. Llewellyn, Thomas H., 910 N. 63rd St. (31)
1907. Lodholz, Edward, The Fairfax, 43rd & Locust Sts. (4)
1958. Loftus, Thomas A., 1025 Walnut St. (7)
1951. Long, Joseph P., 1930 Chestnut St. (3)
1935. Long, William L., 2038 Locust St. (3)
1931. Longaker, Edwin P., 41 E. Montgomery Ave., Ardmore, Pa.

1951. Lorber, Stanley H., 3701 N. Broad St. (40)
1960. Lovett, B. Frank, 618 Benson St., Camden, N. J.
1936. Lucchesi, Pascal Francis, 601 E. Gorgas Lane (19)
1960. Lucine, Albert A., 345 S. 19th St. (3)
1932. Lukens, Francis D. W., Univ. of Pa. Hospital (4)
1939. Luongo, Romeo A., 2054 Locust St. (3)
1947. Lurie, Max B., Henry Phipps Institute, Univ. of Pa. (4)
1951. Luscombe, Herbert A., 136 S. 16th St. (2)
1952. Lutman, Frank C., 100 W. Coulter St. (44)
1950. Lynch, J. Edward, 23 E. Wynnewood Rd., Wynnewood, Pa.
1953. Lyons, John W., 255 S. 17th St. (3)
1952. McCabe, Edward S., 136 S. 16th St. (2)
1932. McCahey, James F., Rittenhouse-Claridge, 18th & Walnut Sts. (3)
1958. McClenahan, John L., 39 E. Chestnut Hill Ave. (18)
1935. McClenahan, William U., 33 East Chestnut Hill Ave., Chestnut Hill (18)
1953. McCloskey, Joseph F., Jefferson Hospital. (7)
1955. McClure, Carroll R., 17 S. Church St., W. Chester, Pa.
1957. McConnell, Edward L., Jr., 2342 S. Broad St. (45)
1934. McCough, Grayson P., Univ. of Pa. School of Medicine (4)
1938. McCrea, Lowrain E., 1930 Chestnut St. (3)
1958. McCune, Wallace G., Germantown Hospital (44)
1937. McCutcheon, Morton, Cambridge Apts. (44)
1942. McDonald, P. Robb, Lankenau Medical Bldg. (51)
1953. McDonnell, William V., 1025 Walnut St. (7)
1952. McElroy, Robert C., 133 S. 36th St. (4)
1950. McFadden, William M., 1187 E. Washington Lane (38)
1949. McGavic, John S., 601 Montgomery Ave., Bryn Mawr, Pa.
1945. McGee, Lemuel Clyde, Hercules Powder Company, Wilmington, Del.
1954. McGehee, Edward H., 33 E. Chestnut Hill Ave. (18)
1952. McGlade, Thomas H., 719 Cooper St., Camden, N. J.
1956. McGrath, Raymond J., 1720 Spruce St. (3)
1959. McKeown, John J., 1012 Walnut St. (7)
1933. McLaughlin, James S., 330 S. 9th St. (7)
1924. McMillan, Thomas M., 1901 Walnut St. (3)
1924. McPhedran, F. Maurice, Germantown Hosp., Penn and Chew Sts. (44)
1955. McStravog, Lawrence J., 6910 Market St., Upper Darby, Pa.
1954. MacFadyen, Bruce V., 135 S. 18th St. (3)
1943. Macfarlan, Douglas, 1805 Chestnut St. (3)
1932. Macfarlane, Catherine, 136 S. 16th St. (2)
1947. Machella, Thomas E., Univ. of Pa. Hospital (4)
1950. Mackmull, Gulden, Greene & Coulter Sts. (44)
1949. MacNeal, Perry Scott, 330 S. 9th St. (7)
1951. Mac Neish, W. J., 136 S. 16th St. (2)
1955. Macy, Dorothy, Jr., 705 Beechwood Road, Media, Pa.
1957. Madow, Leo, 111 N. 49th St. (39)
1935. Maeder, LeRoy M. A., 1910 Rittenhouse Sq. (3)
1952. Mahoney, J. Francis, 250 S. 18th St. (3)
1959. Mandel, Martin M., 255 S. 17th St. (3)
1942. Manges, Lewis C., Jr., 2001 Delancey Place (3)
1954. Manges, Willis E., Methodist Hospital, Broad & Wolf Sts. (48)
1959. Maniglia, Rosario, 230 N. Broad St. (2)
1949. Manlove, Francis R., 406 Surburban Sq., Ardmore, Pa.
1936. Mann, Bernard, 2019 Pine St. (3)

1960. Manning, Valentine R., 3336 Aldine St. (36)
1956. Manstein, George, 1351 Tabor Rd. (41)
1953. Marbach, A. Herbert, 1307 Tabor Rd. (41)
1948. Marden, Philip Ayer, 1910 Spruce St. (3)
1937. Margolies, Alexander, 1351 Tabor Rd. (41)
1958. Marino, Daniel J., 1422 Race St. (2)
1950. Mark, George E., 3401 N. Broad St. (40)
1950. Marshall, E. Wayne, Jr., 1520 Spruce St. (2)
1951. Martin, William L., Hahnemann Hospital. (2)
1952. Martucci, Albert A., 1460 E. Cheltenham Ave. (24)
1953. Marx, Halvey E., 76 Brennan Drive, Bryn Mawr, Pa.
1953. Massey, Franklin C., 122 Hillside road, Deepdale, Strafford, Pa.
1935. Matthews, Robert A., 1025 Walnut St. (7)
1939. May, Hans, 255 S. 17th St. (3)
1951. Mayock, Robert L., 3600 Spruce St. (4)
1958. Mays, Ralph Whiteman, 154 W. Tulpehocken St. (44)
1952. Mecray, Paul, Jr., 405 Loucroft Ave., Haddonfield, N. J.
1951. Medinger, Frederick G., 1941 Woodland Road, Abington, Pa.
1959. Medoff, Joseph, 5400 Wynnefield Ave. (31)
1955. Melnick, Theodore, 1152 N. 63rd St. (31)
1941. Mendell, Theodore H., 2023 Spruce St. (3)
1951. Mendelssohn, Edwin, 1301 Tabor Rd. (41)
1943. Meranze, David R., 1031 Lakeside Ave. (26)
1954. Mertens-Roesler, Elizabeth, 224 W. School House Lane (44)
1956. Merves, Louis, 1930 Chestnut St. (3)
1955. Mervine, Thomas B., 133 S. 36th St. (4)
1959. Metzger, Harry N., 1815 Pine St. (3)
1955. Meyer, Eugene A., 1438 Mt. Ephraim Ave., Camden, N. J.
1937. Meyer, George Phillip, 410 Haddon Ave., Camden, N. J.
1956. Miller, Bernard Joseph, 340 S. 15th St. (3)
1935. Miller, Ford A., 4016 Chestnut St. (4)
1939. Miller, Malcolm W., Lankenau Medical Bldg. (51)
1939. Miller, Merle M., 6013 Greene St. (44)
1932. Miller, M. Valentine, 114 W. Phil-Ellena St. (19)
1921. Miller, T. Grier, 133 S. 36th St. (4)
1955. Miller, William H., Fitzgerald Mercy Hospital, Darby, Pa.
1952. Minehart, John R., 4821 Germantown Ave. (44)
1952. Mintz, S. S., 1930 Chestnut St. (3)
1937. Missett, Joseph Vincent, Jr., 2031 Locust St. (3)
1904. Mitchell, Charles Franklin, 2003 Pine St. (3)
1950. Mitchell, John McK., Univ. of Pa. School of Medicine (4)
1952. Mitchell, Robert McNair, 330 S. 9th St. (7)
1959. Mitterling, Robert C., Chestnut St. & Glendale Rd.; Upper Darby
1932. Mohler, Roy W., 1806 Spruce St. (3)
1936. Montgomery, Hugh, 119 Glenn Road, Ardmore, Pa.
1936. Montgomery, John B., 1930 Chestnut St. (3)
1932. Montgomery, Thaddeus L., 2031 Locust St. (3)
1935. Moore, John Royal, 3401 N. Broad St. (40)
1947. Moore, Matthew Thibaud, 1813 Delancey Pl. (3)
1958. Moore, Samuel R., Jr., 1600 Arch St. (1)
1958. Morani, Alma D., 3665 Midvale Ave. (29)
1936. Morgan, David R., Jefferson Medical College (7)
1944. Morris, Harold H., Villa Nova, Pa.

1945. Morris, I. Paul, 1939 Cheltenham Ave. (17)
1957. Moyer, David G., 701 W. Main St., Lansdale, Pa.
1959. Moyer, John H., 230 N. Broad St. (2)
1941. Mucklé, Craig Wright, 6 Craig Lane, Haverford, Pa.
1929. Mudd, Stuart, Department of Bacteriology, Univ. of Pa. School of Medicine. (4)
1960. Mulberger, Robert D., 1930 Chestnut St. (3)
1949. Mulholland, Stanford W., 22nd & Parkway. (3)
1934. Mullen, Edward A., 472 Roxborough Ave. (28)
1930. Murphy, Douglas P., 601 S. Bowman Ave., Merion Station, Pa.
1953. Murphy, Edward J., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Murphy, John J., 3600 Spruce St. (4)
1959. Murray, Edwin N., 130 N. Broadway, Camden, N. J.
1955. Murtagh, Frederick, 3701 N. Broad St. (40)
1951. Myers, David, 3701 N. Broad St. (40)
1955. Nachod, Grace R., 5501 Greene St. (44)
1945. Naide, Meyer, 2034 Spruce St. (3)
1951. Naidoff, David, 3500 Tudor St. (36)
1950. Nardone, Anthony A., 912 S. 49th St. (43)
1959. Neal, Hunter, S., 406 Lankenau Medical Bldg., (51)
1958. Nealon, Thomas F., Jr., 1025 Walnut St. (7)
1948. Neese, Paul H., 17 Derwen Road, Cynwyd, Pa.
1936. Nelson, Guy M., 255 S. 17th St. (3)
1943. Nelson, Waldo E., 615 Moreno Rd., Narberth, Pa.
1955. Nemir, Paul, Jr., 419 S. 19th St. (46)
1935. Nicholson, Jesse Thompson, 1740 Bainbridge St. (46)
1960. Nicholson, John W., III, 115 Chestnut St., Moorestown, N. J.
1947. Noone, Ernest L., 4501 Cedar Lane, Drexel Hill, Pa.
1905. Norris, Charles C., Darby and Goshen Roads, Bryn Mawr, Pa.
1954. Norris, Charles M., 3401 N. Broad St. (40)
1905. Norris, George W., 250 S. 18th St. (3)
1938. Norris, Robert F., 513 Wynnewood Ave., Wynnewood, Pa.
1957. Oakey, Richard S., Jr., 309 Medical Bldg., Lankenau Hospital (51)
1947. O'Keefe, John J., 255 South 17th St. (3)
1954. Olsen, Axel K., 230 N. Broad St. (2)
1913. O'Neal, Alexander Hay, St. Davids, Pa.
1949. O'Neill, James F., 140 Roslyn Ave., Glenside, Pa.
1954. O'Neill, Thomas J. E., Centennial Bldg., Front St. & Lehigh Ave. (25)
1947. Ornsteen, A. M., 2007 Delancey Pl. (3)
1947. Ornston, Darius Gray, 415 Dresher Road, Horsham, Pa.
1936. Orr, Theodore E., 3815 Chestnut St. (4)
1958. O'Sullivan, Ward D., Misericordia Hospital (43)
1955. Ottenberg, Donald J., 3519 N. Broad St. (40)
1913. Outerbridge, George W., 1927 Spruce St. (3)
1961. Owen, Barbara J., Bryn Mawr Hospital, Bryn Mawr, Pa.
1949. Padis, Nicholas, Lankenau Medical Bldg. (51)
1954. Palmer, Louis H., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1909. Parish, Benjamin Dores, 704 Bethlehem Pike, Flourtown, Pa.
1945. Park, Felix Roman, 1980 Utica Sq., Tulsa, Okla.
1940. Parker, Alan P., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1948. Parkhurst, Leonard Woods, 330 S. 9th St. (7)
1952. Paxson, Newlin F., 250 S. 18th St. (3)
1932. Payne, Franklin L., Univ. of Pa. Hospital. (4)
1954. Pearce, Alexander E., 1420 Race St. (2)

1958. Pearce, Rowan C., Jr., 514 Cooper St., Camden, N. J.
1943. Pearson, Gerald H. J., Presidential Apts.—Adams House. (31)
1954. Pearson, Manuel M., 111 N. 49th St. (39)
1952. Peck, Roy I., 3400 Spruce St. (4)
1960. Peltz, William L., 111 N. 49th St. (39)
1930. Pendergrass, Eugene P., Univ. of Pa. Hospital. (4)
1959. Pendergrass, Henry P., 3400 Spruce St. (4)
1953. Penneys, Raymond, University of Pennsylvania Hospital (4)
1914. Pepper, O. H. Perry, 945 Parks Run Lane, Villanova, Pa.
1916. Percival, Milton Fraser, 2332 S. Broad St. (45)
1942. Perkins, William Harvey, The Lenox, 13th & Spruce Sts. (7)
1946. Perloff, William Harry, 3521 N. Broad St. (40)
1953. Persky, Abram H., 1737 Chestnut St. (3)
1940. Pessel, Johannes F., 224 West State St., Trenton, N. J.
1952. Peters, Michael, 262 W. Broad St., Telford, Pa.
1940. Pettit, Horace, Times Medical Bldg., Ardmore, Pa.
1949. Pettit, Mary DeWitt, 3343 W. Penn St. (29)
1915. Pfeiffer, Damon B., Meadowbrook, Pa.
1946. Pfeiffer, Mildred C. J., 358 Valley Rd., Merion, Pa.
1935. Phillips, Arthur W., 3904 Walnut St. (4)
1911. Piersol, George Morris, 308 Kent Rd., Wynnewood, Pa.
1948. Pierson, Daniel B., Jr., 740 Beacon Lane, Merion, Pa.
1961. Pike, Anne H., 5603 Greene St. (44)
1957. Pilling, George Platt, IV, 2600 N. Lawrence St. (33)
1933. Pillsbury, Donald M., Univ. of Pa. Hospital (4)
1950. Pincus, Irwin J., Cedars of Lebanon Hospital, Los Angeles, Cal.
1957. Platt, Ruth M., 441 Lyceum Ave. (28)
1951. Poinsard, Paul J., 2031 Locust St. (3)
1937. Polk, David Stewart, Rosemont, Pa.
1956. Pontarelli, Domenic J., Rittenhouse Plaza, 1901 Walnut St. (3)
1953. Porreca, George A., 1912 Spruce St. (3)
1932. Porter, Roland De Lance, Abington Medical Bldg., Abington, Pa.
1951. Post, Joseph W., 1930 Chestnut St. (3)
1951. Pote, Harry H., 103 E. Ridley Ave., Ridley Park, Pa.
1958. Potter, H. Phelps, Jr., 3400 Spruce St. (4)
1951. Pressman, Robert S., 170 W. Olney Ave. (20)
1947. Prickett, John A., Warrington, Bucks County, Pa.
1954. Prince, Leon N., 2025 Spruce St. (3)
1931. Pryor, Charles Allen, 255 S. 17th St. (3)
1952. Pugh, James E., 614 Church Lane, Yeadon, Pa.
1947. Putney, Floyd Johnson, 1712 Locust St. (3)
1958. Rachlin, Lillian, Veterans' Adm. Hosp., Sepulveda, Cal.
1943. Radbill, Samuel X, 7043 Elmwood Ave. (42)
1953. Radbill, Sidney G., 37 S. 20th St. (3)
1945. Rakoff, Abraham Edward, 269 S. 19th St. (3)
1953. Ralston, Edgar L., 3400 Spruce St. (4)
1931. Ramsey, Frank M., 620 E. Willow Grove Ave. (18)
1953. Ranieri, Tito A., 2320 S. Broad St. (45)
1941. Rankin, Charles A., Ludlow & Heather Rd., Upper Darby, Pa.
1946. Rapaport, Milton, Children's Hospital, 1740 Bainbridge St. (46)
1951. Rathmell, Thomas K., 446 Bellevue Ave., Trenton, N. J.
1926. Ravdin, I. S., Univ. of Pa. Hospital. (4)
1956. Ravdin, Robert Glenn, 3400 Spruce St. (4)

1959. Raventos, Antolin, 3400 Spruce St. (4)
1954. Reagan, Lindley B., 175 Madison Ave., Mt. Holly, N. J.
1960. Reed, Theodore P., Lankenau Medical Bldg. (51)
1928. Reese, Warren S., 2118 Locust St. (3)
1920. Rehfuss, Martin E., 131 St. George's Rd., Ardmore, Pa.
1921. Reiff, E. Paul, 1927 Spruce St. (3)
1919. Reimann, Stanley P., 703 W. Phil-Ellena St. (19)
1956. Reishtein, William A., 255 S. 17th St. (3)
1951. Rentschler, Laurence B., 5800 Ridge Ave. (28)
1945. Rhoads, Jonathan E., Univ. of Pa. Hospital (4)
1951. Richardson, Fred Mac D., 160 Carpenter Lane (19)
1919. Richardson, Russell, Phila. Tuberculosis Sanitorium #4, Corinthian & Girard Aves. (30)
1951. Riegel, Donald, 5110 Chester Ave. (43)
1942. Riggs, Helena E., 150 Hewitt Rd., Wyncote, Pa.
1936. Ritter, Joseph A., 2405 N. 54th St. (31)
1932. Robbins, Frederick R., 317 Milbank Rd., Bryn Mawr, Pa.
1952. Robbins, Robert, 3401 N. Broad St. (40)
1960. Robbins, William S., 255 S. 17th St. (3)
1954. Roberts, Brooke, 3400 Spruce St. (4)
1939. Roberts, Ella, 133 S. 36th St. (4)
1957. Roberts, Joan Mary, 4 W. Mt. Pleasant Ave. (19)
1932. Robertson, Harold F., 2118 Pine St. (3)
1954. Robertson, Hugh, 255 S. 17th St. (3)
1938. Roche, Philip Q., Route 1, Conshohocken, Pa.
1960. Roeder, Paul H., 330 S. 9th St. (7)
1955. Rogers, Fred B., 3401 N. Broad St. (40)
1951. Ronis, Bernard J., 2106 Spruce St. (3)
1948. Roscoe, Constantine R., 7226 Castor Ave. (24)
1928. Rose, Edward, 426 Owen Rd., Wynnewood, Pa.
1936. Rose, Elizabeth Kirk, 426 Owen Rd., Wynnewood, Pa.
1959. Rose, Isadore, 6000 W. Oxford St. (31)
1952. Rose, S. Brandt, Chestnut Hill Hospital (18)
1946. Rosemond, George Parrott, 3401 N. Broad St. (40)
1960. Rosenow, Edward C., Jr., American College of Physicians, 4200 Pine St. (4)
1948. Rothman, Maurice M., 1727 Spruce St. (3)
1951. Rouse, George P., Jr., 2031 Locust St. (3)
1952. Roxby, Bruce S., 5501 Greene St. (44)
1955. Roxby, John B., Jr., 4821 Germantown Ave. (44)
1949. Royster, Henry P., 3400 Spruce St. (4)
1941. Royster, Hubert A., Jr., 888 Glenbrook Ave., Bryn Mawr, Pa.
1959. Rubin, Alan, 255 S. 17th St. (3)
1952. Rubin, I. Edward, 255 S. 17th St. (3)
1933. Rudolphy, Jay Besson, 230 S. 21st St. (3)
1946. Rupp, Charles, 133 S. 36th St. (4)
1947. Rush, Alexander, 330 S. 9th St. (7)
1960. Russell, George W., 430 Greenwood Ave., Wyncote, Pa.
1945. Rynes, Samuel E., 334 S. 21st St. (3)
1952. Sain, Fletcher D., 8 Orchard Ave., Bristol, Pa.
1958. Sall, Manuel, 255 S. 17th St. (3)
1952. Salner, Nathan P., 6812 Castor Ave. (24)
1952. Saltzman, Maurice, 2037 Spruce St. (3)
1944. Sampson, David Alan, 726 Braeburn Lane, Penn Valley, Narberth, Pa.
1936. Sands, Joseph Evans, Rosemont, Pa.

1950. Sarner, Joseph B., 269 S. 19th St. (3)
1949. Saul, Leon J., Highland Ave., Media, Pa.
1908. Sautter, Albert C., Germantown Professional Bldg. (44)
1954. Savacool, J. Woodrow, 146 W. Tulpehocken St. (44)
1947. Saÿen, John J., 3600 Spruce St. (4)
1948. Scarano, Joseph Albert, 1432 S. Broad St. (46)
1917. Schaeffer, J. Parsons, 4634 Spruce St. (39)
1929. Scheffey, Lewis C., 601 Walnut Lane, Haverford, Pa.
1942. Scheie, Harold G., 3400 Spruce St., (4)
1929. Schenck, Harry P., 1235 Wyngate Rd., Wynnewood, Pa.
1945. Schlezinger, Nathan S., 255 S. 17th St. (3)
1961. Schlosser, Woodrow D., 3701 N. Broad St. (40)
1917. Schnabel, Truman G., 1704 Pine St. (3)
1958. Schnabel, Truman G., Jr., Phila. General Hospital (4)
1957. Schnall, Nathan, 2037 Pine St. (3)
1928. Schofield, Frederick S., 1509 E. Barringer St. (50)
1955. Schreader, Charles J., 318 W. Godfrey Ave. (20)
1958. Schreck, Kenneth M., Temple Univ. School of Medicine (40)
1952. Schulz, Norbert J., 1901 Walnut St. (3)
1950. Schumann, Francis N., 8811 Germantown Ave. (18)
1948. Schwarz, Gabriel A., 133 S. 36th St. (4)
1955. Schwegman, Cletus W., Hospital of the University of Penna. (4)
1930. Scott, John Porter, Children's Hospital, 1740 Bainbridge St. (46)
1950. Scott, Michael, 3401 N. Broad St. (40)
1940. Scott, T. F. McNair, Children's Hospital, 1740 Bainbridge St. (46)
1952. Seifer, Arthur F., 3401 N. Broad St. (40)
1954. Seifter, Joseph, Wyeth Institute for Medical Research (1)
1957. Seipel, Russell C., 6000 Jefferson St. (31)
1951. Seitchik, Joseph N., 1417 Race St., Hahnemann Medical College Annex (2)
1958. Sellers, Alfred M., Hosp. of the Univ. of Pa. (4)
1952. Semisch, Charles W., III, 5329 Rising Sun Ave. (20)
1961. Sencindiver, Paige V., 2228 S. Broad St. (45)
1958. Shafer, Albert H., 1004 E. Cherry Hill Apts., Merchantsville 10, N. J.
1960. Shannon, Gerard M., 1434 E. Hunting Park Ave. (24)
1950. Sharp, Reuben L., 719 Cooper St., Camden, N. J.
1928. Sharpless, Frederick C., 621 Railroad Ave., Haverford, Pa.
1956. Shaw, Daniel L., Jr., 702 Knox Rd., Villanova, Pa.
1948. Shay, Harry, 3400 N. Broad St. (40)
1955. Shechter, Fred R., 2461 No. 54th St. (31)
1954. Shelley, Walter B., 36th & Spruce Sts. (4)
1955. Shenkin, Henry A., Episcopal Hospital (25)
1946. Shepherd, Samuel Garfield, 2039 Pine St. (3)
1932. Sheridan, Joyce T., 412 W. Durham St. (19)
1956. Sherson, Jacob S., 131 Channing Ave., Malvern, Pa.
1936. Shipman, James Shelby, 255 S. 17th St. (3)
1958. Shipps, Hammell P., 719 Cooper St., Camden 2, N. J.
1957. Shope, Edward Pierce Lentz, 807 Wilson Bldg., Camden, N. J.
1946. Shoup, George Daniel, 121 W. Walnut Lane (44)
1955. Shubin, Harry, 6601 N. 21st St. (38)
1952. Shuman, Charles R., 3401 N. Broad St. (40)
1936. Shuster, Benjamin H., 1824 Pine St. (3)
1949. Sidlick, David M., 255 S. 17th St. (3)
1941. Silcox, Louis E., Lankenau Medical Bldg. (51)

1956. Sillars, Charles H., Abington Memorial Hospital, Abington, Pa.
1955. Silverstein, Alexander, 2114 Pine St. (3)
1954. Singmaster, Lawrence, Lankenau Medical Bldg. (51)
1952. Skromak, Stanley J., 5108 Torresdale Ave. (35)
1958. Sloviter, Henry A., 3400 Spruce St. (4)
1929. Smith, Austin T., 330 S. 9th St. (7)
1955. Smith, J. Winslow, 3034 Darby Rd., Ardmore, Pa.
1933. Smith, Lauren Howe, 111 N. 49th St. (39)
1952. Smith, Richard T., 330 S. 9th St. (7)
1927. Smyth, Calvin Mason, Abington Memorial Hospital, Abington, Pa.
1951. Snape, William J., 573 Stevens St., Camden, N. J.
1938. Snodgrass, L. E., 709 Walnut St. (6)
1953. Snyder, G. Gordon, Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1958. Sodeman, William A., 1025 Walnut St. (7)
1935. Sokoloff, Martin J., 255 S. 17th St. (3)
1951. Solis-Cohen, Leon, 1530 Locust St. (2)
1940. Soloff, Louis A., 3401 N. Broad St. (40)
1950. Somerville, William J., 37 S. 20th St. (3)
1944. Sommer, George N. J., Jr., 120 W. State St., Trenton, N. J.
1952. Sones, Maurice, Mt. Airy Medical Bldg. (19)
1951. Sonneborn, Duane G., 1200 W. Erie Ave. (24)
1928. Spaeth, Edmund B., 1930 Chestnut St. (3)
1958. Spaeth, Philip G., 1930 Chestnut St. (3)
1937. Spangler, John Luther, Devon, Pa.
1957. Spelman, Joseph Worcester, Dept. of Public Health, 13th & Wood Sts. (7)
1935. Spiegel, Ernest A., 6807 Lawnton Ave. (26)
1955. Spitz, Eugene B., Children's Hospital (46)
1958. Splendido, Joseph A., 608 W. Clivedon (19)
1961. Stahlgren, LeRoy H., 133 S. 36th St. (4)
1960. Stainback, William C., Bryn Mawr Medical Bldg., Bryn Mawr, Pa.
1957. Stanley, Robert C. G., 2315 Edgemont Rd., Chester, Pa.
1927. Starr, Isaac, 505 Cresheim Valley Rd. (18)
1952. Stauffer, Herbert M., 3401 N. Broad St. (40)
1952. Stayman, Joseph W., Jr., Germantown Hospital (44)
1945. Stecher, H. Armin, 1510 Darby Rd., Havertown, Pa.
1955. Steel, Howard H., 3401 N. Broad St. (40)
1952. Steiger, William A., 3401 N. Broad St. (40)
1946. Stein, Irvin, 1936 Spruce St. (3)
1953. Stein, Raymond O., 269 S. 19th St. (3)
1936. Steinfield, Edward, N.E. Cor. 18th and Chestnut Sts. (3)
1951. Sterling, Julian A., 1008 Sharpless Rd. (26)
1948. Stevens, Lloyd W., 133 S. 36th St. (4)
1925. Stokes, John H., 4228 Spruce St. (4)
1928. Stokes, Joseph, Jr., Children's Hospital, 1740 Bainbridge St. (46)
1943. Stokes, S. Emlen, 129 Chester Ave., Moorestown, N. J.
1954. Stone, Hrant H., E. Shawmont Ave. (28)
1952. Stoner, Emery K., 222 E. Mt. Pleasant Ave. (19)
1953. Strawbridge, Rendall R., Lankenau Medical Bldg. (51)
1937. Strumia, Max M., Penn Valley, Narberth, Pa.
1960. Strumia, Paul V., Bryn Mawr Hospital, Bryn Mawr, Pa.
1937. Sturgis, Margaret C., 349 Wistar Rd., Wynnewood, Pa.
1927. Sturgis, Samuel Booth, 349 Wistar Rd., Wynnewood, Pa.
1961. Sullivan, Andrew A., 5455 Trinity Place (43)

1934. Summey, Thomas J., Burlington County Hosp., Mt. Holly, N. J.
1930. Sunderman, F. William, 1833 Delancey Place (3)
1936. Surver, James Miller, 1618 Locust St. (3)
1954. Sussman, Marcel S., 101 S. 20th St. (3)
1952. Sweeney, Francis X., 2412 E. Allegheny Ave. (34)
1955. Taggart, Harold A., 235 N. 15th St. (2)
1952. Talbot, Timothy R., Jr., 204 Booth Lane, Haverford, Pa.
1943. Tassman, Isaac S., 136 S. 16th St. (2)
1946. Tauber, Robert, 2019 Walnut St. (3)
1952. Taylor, Ann Gray, 6364 Germantown Ave. (44)
1960. Taylor, Daniel B., 2241 Federal St. (46)
1956. Templeton, John Y., III, 1025 Walnut St. (7)
1951. Theodos, Peter A., 1930 Chestnut St. (3)
1961. Therman, Per-Olof, 111 N. 49th St. (39)
1959. Thomas, Arthur H., 5240 Vine St. (39)
1946. Thomas, Carmen C., 1930 Chestnut St. (3)
1952. Thompson, Charles M., 255 S. 17th St. (3)
1961. Thompson, James C., 803 Spruce St. (7)
1927. Thorington, J. Monroe, 37 S. 20th St. (3)
1936. Thorp, Francis Quicksall, 4900 Penn St. (24)
1936. Thudium, William J., 700 Merion Square Rd., Gladwyne, Pa.
1954. Tindall, Dorothy D., 37 S. 20th St. (3)
1935. Tocantins, Leandro Maués, 1025 Walnut St. (7)
1935. Toland, Owen J., Episcopal Hospital, Front and Lehigh Aves. (25)
1952. Tondreau, Roderick L., 6470 Drexel Rd. (31)
1959. Toole, James F., Univ. of Pa. Hospital, 3400 Spruce St. (4)
1949. Tornay, Anthony S., 2038 Locust St. (3)
1945. Tourish, William J., 1124 Woodmont Rd., Gladwyne, Pa.
1936. Towson, Charles Emory, 224 W. Washington Lane (44)
1955. Trimpi, Howard D., 501 N. 17th St., Allentown, Pa.
1954. Trommer, Philip R., 258 S. 18th St. (3)
1956. Troncelliti, Mario V., Pennsylvania Hospital (7)
1953. Tropea, Frank, Jr., 500 Mulberry Lane, Haverford, Pa.
1947. Trueman, Robert H., 2101 Chestnut St. (3)
1954. Truitt, R. Marshall, Jr., 740 Westview St. (19)
1959. Tuddenham, William J., 3400 Spruce St. (4)
1938. Tuft, Louis, 1530 Locust St. (2)
1933. Tumen, Henry J., 1830 Rittenhouse Square (3)
1938. Turman, Christopher M., Wyncote, Pa.
1923. Turner, Creighton, H., 1731 Pine St. (3)
1954. Turner, Linton W., 3401 N. Broad St. (40)
1929. Tyson, Ralph M., 255 S. 17th St. (3)
1959. Tyson, R. Robert, 3401 N. Broad St. (40)
1937. Uhle, Charles A. W., Lankenau Medical Bldg. (51)
1953. Ulin, Alexander, W., 230 N. Broad St. (2)
1907. Ullom, Josephus T., Carpenter and Quincy Sts. (19)
1960. Uricchio, Joseph F., 1422 Race St. (2)
1950. Valdes-Dapena, Antonio, 3006 Midvale Ave., Phila. (29)
1958. Van den Noort, Gordon S., 888 Glenbrook Ave., Bryn Mawr, Pa.
1937. Vander Veer, Joseph B., 330 S. 9th St. (7)
1937. Van Loon, Emily Lois, 1930 Chestnut St. (3)
1960. Van Meter, Ralph H., 244 W. Main St., Moorestown, N. J.
1933. Vastine, Jacob H., 2nd, 136 S. 16th St. (2)

1958. Velkoff, Cyril L., 2100 Walnut St. (3)
1955. Viek, Peter, 1941 Woodland Rd., Abington, Pa.
1952. Vischer, Thomas J., 5903 Greene St. (44)
1940. Voegelin, Adrian W., Germantown Professional Bldg. (44)
1941. Vogel, Stoughton R., 151 W. Tulpehocken St. (44)
1960. Wagenheim, Harry H., 1822 Spruce St. (3)
1949. Wagner, Frederick B., Jr., 800 Chauncy Road, Narberth, Pa.
1949. Wagner, Joseph A., 201 Highland Ave., Bryn Mawr, Pa.
1954. Wainer, Amos S., 1621 Spruce St. (2)
1938. Waldman, Joseph, 404 Meadowbrook Lane (18)
1955. Waldron, Jerome M., 2300 Cheltenham Ave. (50)
1932. Walkling, Adolph A., 136 S. 16th St. (2)
1955. Warner, Halsey F., 100 W. Coulter St. (44)
1956. Watkins, E. Lloyd, 8815 Germantown Ave. (18)
1954. Waugh, Elizabeth S., 348 Green Lane (28)
1952. Weaver, Harry S., Jr., 37 S. 20th St. (3)
1955. Weaver, Robert L., 26 Henley Rd. (31)
1953. Weber, Lennard L., 255 S. 17th St. (3)
1957. Webster, Marie Blanchefield, 2128 Van Ness Ave., San Francisco 9, Cal.
1930. Weeder, S. Dana, 250 W. Tulpehocken St. (44)
1954. Weiner, Louis H., Carlene Apts. 2500 Belmont Ave. (31)
1952. Weinstein, George L., 255 S. 17th St. (3)
1950. Weiss, Sidney, 1930 Chestnut St. (3)
1959. Wellenbach, Burton L., 255 S. 17th St. (3)
1951. Welty, Jack W., Montgomery Ave. & Owen Rd., Wynnewood, Pa.
1955. Wendkos, Martin H., Latches Lane Apts., Merion, Pa.
1959. West, Clifton F., Jr., 406 Lankenau Medical Bldg. (51)
1959. Whayne, Tom F., 36th & Spruce Sts. (4)
1935. Whelan, G. L., 2100 Walnut St. (3)
1921. Whitaker, William, 4645 Oakland S. (24)
1936. White, Ellen Pawling Corson-, Gladwyne, Pa.
1960. Whiteley, William H., 1015 Chestnut St. (7)
1925. Widmann, Bernard P., 250 S. 18th St. (3)
1954. Wieder, Henry S., Jr., 330 S. 9th St. (7)
1939. Willauer, George, 6129 Greene St. (44)
1937. Williams, John C., 6370 Germantown Ave. (44)
1920. Williams, Philip F., 256 Broughton Lane, Villanova, Pa.
1950. Williams, R. G., Univ. of Pa. School of Medicine (4)
1927. Williamson, Ernest G., 6353 Woodbine Ave. (31)
1949. Willson, J. Robert, 3401 N. Broad St. (40)
1945. Wilson, John F., 2013 Delancey Pl. (3)
1937. Wilson, Ross B., Lankenau Medical Bldg. (51)
1949. Wilson, William W., 133 S. 36th St. (4)
1957. Winkelman, N. William, Jr., 1930 Chestnut St. (3)
1948. Winston, Julius, 5839 Chester Ave. (43)
1941. Wirts, C. Wilmer, 2017 Delancey St. (3)
1953. Wohl, George T., 1227 Remington Rd., Wynnewood, Pa.
1933. Wohl, Michael G., 1727 Pine St. (3)
1958. Woldow, Irving, Einstein Med. Center, York & Tabor Rds. (41)
1958. Wolf, John H., 124 W. Walnut Lane (44)
1944. Wolf, Lewis R., 3474 Frankford Ave. (34)
1918. Wolferth, Charles C., 133 S. 36th St. (4)
1957. Wolgamot, John R., 244 W. Main St., Moorestown, N. J.

1957. Wolkowicz, Michael I., 2022 Spruce St. (3)
1942. Wolman, Irving J., 7607 Woodlawn Ave. (26)
1950. Wood, Dorothy D., 2035 Walnut St. (3)
1932. Wood, Francis C., 212 Laurel Lane, Haverford, Pa.
1944. Wood, H. Curtis, Jr., Skippack Pk., Whitemarsh, Pa.
1953. Woodruff, Marston T., 4940 Penn St. (24)
1928. Wright, Carroll S., 1402 Spruce St. (2)
1960. Wurzel, Harold A., 3400 Spruce St. (4)
1960. Yanoff, Jacob, 1000 Johnston St. (48)
1921. Ylvisaker, Lauritz S., 429 Montgomery Ave., Haverford, Pa.
1941. Young, Barton R., Germantown Hospital (44)
1953. Zarafonetis, Chris J. D., Simpson Memorial Institute, Univ. of Michigan, Ann Arbor, Michigan
1957. Zaslow, Jerry, 1351 Tabor Rd. (41)
1955. Zatuchni, Jacob, 3401 N. Broad St. (40)
1946. Zeigerman, Joseph H., 2105 Spruce St. (3)
1949. Zintl, William J., 69th & Market Sts., Upper Darby, Pa.
1956. Ziserman, Abraham J., 2046 Pine St. (3)
1933. Zulick J. Donald, Abington Memorial Hospital, Abington, Pa.

Non-Resident Fellows

ELECTED

1912. Addison, William H. F., 286 East Sidney Avenue, Mt. Vernon, N. Y.
1947. Allbritten, Frank F., Jr., Univ. of Kansas Medical Center, Kansas City 3, Kansas.
1960. Ames, Mary Daniel, 2039 N. 2nd St., Harrisburg, Pa.
1941. *Aronson, Roland S., 9401 Byeforde Road, Kensington, Md.
1954. Austin, George M., University of Oregon Medical School, Portland, Oregon
1934. Bank, Joseph, 800 N. First Ave., Phoenix, Arizona
1931. Bates, William, Harrisburg Hospital, Harrisburg, Pa.
1932. Behney, Charles A., Dept. of Health, Old DeWitt Rd., Lansing, Mich.
1955. Blank, Harvey, Jackson Memorial Hospital, Miami 36, Fla.
1921. Borzell, Francis F., R. D. 2, Box 2051, Browns Mills, N. J.
1937. Braceland, Francis J., The Institute of Living, 200 Retreat Ave., Hartford, Conn.
1951. Brinton, S. Jervis, 245 Coral Lane, Palm Beach, Fla.
1948. *Brown, Robert B., U. S. Naval Hospital, Bethesda, Md.
1953. Burbidge, J. Raymond, 163 Nassau St., Princeton, N. J.
1957. Butterworth, Thomas, 411 Walnut St., Reading, Pa.
1948. Chapman, John P., Calle Fray Junipero Serra 26, Palma de Mallorca, Balearic Islands, Spain.
1950. Chapple, Charles C., 1500 Massachusetts Ave., N.W., Washington, D. C.
1941. Cheleden, John, 1012 Volusia Ave., Daytona Beach, Fla.
1930. Clarke, Francis Mann, 116 New St., New Brunswick, N. J.
1926. Clerf, Louis H., 5575–8th Ave., North, St. Petersburg, Fla.
1930. Cottrell, James E., McGuire Veteran's Administration Hospital, Richmond 19, Va.
1959. *Cowan, Capt. John S., U. S. Atlantic Fleet, P.O. Box 100, Norfolk 11, Va.
1960. Cowley, Allen W., Sr., 1919 N. Front St., Harrisburg, Pa.
1940. Crowe, Aldrich C., 1208 Ocean Ave., Ocean City, N. J.
1947. Cutler, Norman L., 1300 Harrison St., Wilmington, Del.
1941. *Cuttle, Tracy D., Marine Corps Recruit Depot, San Diego (40) Calif.
1955. Daugherty, J. Arthur, 1511 N. Front St., Harrisburg, Pa.

* Military service.

1954. Deitrick, John E., Cornell Medical College, 1300 York Ave., New York 21, N. Y.
1941. Dixon, Harold M., 4805 46th St., N.W., Washington 16, D. C.
1953. Dixon, James P., Antioch College, Yellow Springs, Ohio.
1961. Duane, Thomas D., 619 Main St., Bethlehem, Pa.
1937. Dunn, Charles W., Grange Ave., Collegeville, R.D. #1, Pa.
1959. Durgin, Bernice Elise, 221 N. Allegheny St., Bellefonte, Pa.
1953. Eberhard, Theodore P., St. Joseph Mercy Hosp., Ann Arbor, Mich.
1955. Edwards, Margaret Hay, 1100 Edgewood Ave., Trenton, N. J.
1953. Eisenberg, Isadore J., 1520 N. 2nd St., Harrisburg, Pa.
1951. Ellis, Mackinnon, 121 Mill Rock Rd., Hamden, Conn.
1957. *Errion, Arthur Robbins, U. S. Naval Hospital, St. Albans, New York.
1951. Ervin, Carl E., 240 North Third Street, Harrisburg, Pa.
1944. Estes, W. L., Jr., 35 E. Elizabeth Ave., Bethlehem, Pa.
1954. Evans, Harry D., Jr., American Cyanamid Co., 1 Caspar St., Danbury, Conn.
1952. Faller, Constantine P., 127 State St., Harrisburg, Pa.
1940. Forrester, James S., Harrisburg Polyclinic Hospital, Harrisburg, Pa.
1951. Friedland, Carl K., 271 W. Blackwell St., Dover, N. J.
1947. Gaskill, Herbert S., 250 Ash St., Denver, Colo.
1913. Gates, Nathaniel, 10 Peterboro Ave., Detroit, Mich.
1958. Geckler, George D., Tranquility, S. Windham, Vt.
1957. Giering, John Fleming, 84 James St., Kingston, Pa.
1931. Gilman, Robert Louis, Cheyney, Pa.
1954. Godfrey, Ellwood W., Princeton Hospital, Princeton, N. J.
1928. Gordon, Burgess L., The Lovelace Foundation, Albuquerque, New Mexico.
1952. Grieco, Reynold M., 2 W. 4th St., Williamsport, Pa.
1952. Gross, Elmer R., Medical Arts Bldg., Wilmington, Del.
1933. Gruber, Charles M., 1313 College Ave., Redlands, Calif.
1939. Hamblock, Leonard C., R.D. 2, Mt. Joy, Pa.
1955. Harris, John H., 1301-A N. Second St., Harrisburg, Pa.
1936. Hatch, Lerleen Clement, 2184 Ayres Ave., Akron, Ohio.
1928. Hayman, Joseph Marchant, Jr., Tufts College Medical School, Boston, Mass.
1944. Hershey, J. Ivan, VA Hospital, Shreveport, La.
1955. Hills, Arthur G., 1000 N. W. 17th St., Miami, Fla. (36)
1933. Hitzrot, Lewis H., Medical Director, Mercersburg Academy, Mercersburg, Pa.
1950. Horn, Robert C., Henry Ford Hospital, Detroit, Mich.
1938. Howell, John C., 1104 Logan Ave., Tyrone, Pa.
1936. Hughes, Brady A., 312 Euclid Ave., Mt. Brook, Birmingham, Ala.
1953. Imber, Irving, 428 Walnut St., Reading, Pa.
1958. Impink, Robert R., 405 Oley St., Reading, Pa.
1935. Ingleby, Helen, The Church House, Heacham, King's Lynn, England
1921. Ivy, Robert H., 104 Dalton Rd., Paoli, Pa.
1952. Jones, Ralph, Jr., Jackson Memorial Hospital, Miami, Fla.
1955. Jordan, Charlotte B., 519 Sarah St., Stroudsburg, Pa.
1955. Jordan, Claus G., 519 Sarah St., Stroudsburg, Pa.
1956. Keffer, William H., 413 Oley St., Reading, Pa.
1947. Kelchner, Clyde H., 1125 Turner St., Allentown, Pa.
1930. Kimbrough, Robert A., Jr., 1350 Astor St., Chicago 10, Ill.
1944. LaMotte, William O., Brook Hill Farms, Hockessin, Del.
1954. LaMotte, William O., Jr., Professional Bldg., Wilmington 3, Del.
1952. Levan, John B., 401 Oley St., Reading, Pa.
1949. Lhamon, William T., Baylor University College of Medicine, Houston, Tex.
1954. Light, John J. B., 25 N. 9th St., Lebanon, Pa.
1954. Lindenmuth, Woodrow W., VA Hospital, West Haven, Conn.

1948. Livingood, Clarence S., Henry Ford Hospital, Detroit 2, Mich.
1933. Long, Esmond R., Conifer, Pedlar Mills, Va.
1919. Lynch, Frank B., Jr., U. S. Veterans Hospital, Coatesville, Pa.
1948. McCall, Milton L., Elizabeth Steel Magee Hospital, Pittsburgh Pa. (13)
1954. McCrory, Wallace W., Dept. of Pediatrics, University Hospital, Iowa City, Iowa
1948. McLaughlin, John T., 1252 S. Central Ave., Glendale, Calif.
1953. Margolies, Michael, 567 E. Chestnut St., Coatesville, Pa.
1955. Margolies, M. Price, 567 E. Chestnut St., Coatesville, Pa.
1935. Mason, James B., 40 E. Erie St., Chicago 11, Ill.
1932. Meade, Richard H., Jr., 750 San Jose Dr., Grand Rapids, Mich.
1936. Middleton, William Shainline, Veteran's Administration, Washington, D. C.
1946. Miller, Franklin R., Snyder-Jones Clinic, First Nat. Bk. Bldg., Winfield, Kansas.
1928. Moon, Virgil H., Univ. of Miami, Coral Gables, Fla.
1949. Motley, Hurley L., 1212 Shatto St., Los Angeles, Calif.
1950. Neefe, John R., 627 Eleventh St., St. Petersburg, Fla.
1937. Nicholson, Samuel T., 2d, 642 High St., Pottstown, Pa.
1960. Ojers, Gaylord W., 619 Main St., Bethlehem, Pa.
1956. Oppenheimer, Albert, 224 E. Main St., Moorestown, N. J.
1926. Paul, John Rodman, Dept. Preventive Medicine, Yale University, New Haven, Conn.
1922. Pleasants, Henry, West Chester, Pa.
1953. Raffensperger, Edward C., 2039 N. 2nd St., Harrisburg, Pa.
1938. Read, Hilton S., 5407 Atlantic Ave., Atlantic City, N. J.
1958. Reinhardt, David J., III, 1600 N. Broom St., Wilmington, Del.
1936. Reisinger, John A., 901 20th St., N.W., Washington, D. C.
1955. Rettew, Philip L., 612 Museum Rd., Reading, Pa.
1947. Rogers, Arthur Merriam, 1351 Durwood Drive, Charlotte, N. C.
1907. Royer, B. Franklin, 429 E. Baltimore St., Greencastle, Pa.
1956. Rubenstone, Albert I., Michael Reese Hosp., Chicago, Ill.
1954. Sampson, Martin C., Keydross Lane, Saratoga, N. Y.
1953. Scanlan, Robert L., St. Vincent's Hospital, 2131 W. 3rd St., Los Angeles 57, Calif.
1945. Schell, James F., 139 W. Maple Ave., Langhorne, Pa.
1921. Schumann, Edward A., "Henneberg", Chalfont, Pa.
1913. de Schweinitz, George L., 3231 Arroyo Chico, Tucson, Ariz.
1941. Shands, Alfred R., Jr., Alfred I. duPont Institute, Rockland Rd., Wilmington, Del.
1908. Shannon, Charles E. G., 9 Park St., Waterville, Maine
1950. Shiffer, Paul H., Dreher Ave., R.D. #2, Stroudsburg, Pa.
1951. Shorey, Winston K., 7848 S.W. 120th St., Miami 56, Fla.
1932. Siegel, Alvin Erdreich, 464 W. Buford Rd., Macon, Ga.
1933. Smelzer, Donald C., Lancaster General Hospital, Lancaster, Pa.
1954. Smith, Charles W., 128 State St., Harrisburg, Pa.
1929. Sponsler, Marshall B., 103 Lansdowne Road, DeWitt, N. Y.
1953. Steele, Brandt F., 717 Pontiac St., Denver 20, Colo.
1952. Steele, Eleanor, 717 Pontiac St., Denver 20, Colo.
1942. Stengel, Alfred, Jr., 75 Highland St., Holden, Mass.
1955. Stevenson, Theodore D., Presbyterian Board of Foreign Missions, 156 Fifth Ave., New York 10, N. Y.
1934. Stewart, Sloan G., Pacific and North Carolina Avenues, Atlantic City, N. J.
1931. Stiles, Merritt H., E. 406 14th Ave., Spokane 3, Wash.
1949. Stockwell, Eunice L., Tryon, N. C.
1953. Stroud, Morris W., 3rd, Harvard Rd., Cleveland, Ohio
1944. Swenson, Paul C., Veterans Hosp., Columbia, S. C.
1931. Taylor, Norman H., Queen of the East, E. Broadway, Hamilton, Bermuda.
1928. Thomas, J. Earle, College of Medical Evangelists, School of Medicine, Loma Linda, Calif.

1942. Thompson, Wesley D., 247 E. 3rd St., Lewistown, Pa.
1941. Tompkins, Pendleton, 450 Sutter St., San Francisco, Calif.
1897. Veasey, Clarence A., 1118 W. 9th Ave., Spokane 9, Wash.
1933. Waygood, James L., Pocono Pines, Pa.
1941. Weaver, Ruth H., 108 Atlantic Ave., Atlantic City, N. J.
1936. Wilder, Theodore S., Beckley Memorial Hospital, Beckley, W. Va.
1935. Willard, John H., Harlan Memorial Hospital, Harlan, Kentucky.
1953. Wilson, Julius L., Natl. Tuberculosis Assn., 1790 Broadway, New York City (19)
1957. Witkow, Alexander, 401 Columbia Road, Hamilton, Ohio
1952. Wood, Horatio C., III, 5319 Prospect Rd., Peoria, Ill.
1947. Zintel, Harold A., St. Luke's Hospital, Amsterdam Ave. & 113th St., New York 25, N. Y.

Honorary Fellows

Limited to Fifty, of Whom Twenty May be Foreigners

American

elected

1959. Fay, Marion, B.A., M.A., PH.D., SC.D.(HON.), LL.D.(HON.), Woman's Medical College, Henry Ave. & Abbottsford Rd. (29)
1936. Richards, Alfred Newton, PH.D., SC.D., M.D.(HON.), LL.D., Emeritus Professor of Pharmacology, School of Medicine, and Associate Trustee, University of Pennsylvania.
1958. Shryock, Richard H., PH.D., American Philosophical Society, Independence Square (6)
1947. Stone, Robert Spencer, M.D., University of California Medical School, San Francisco, Cal.

Foreign

1937. Dale, Sir Henry Hallet, C.B.E., F.R.S., M.A., M.D., F.R.C.P., 52 Queen Anne St., London, W. 1, England.
1955. Mann, Ida, M.A., D.SC., M.B., B.S., L.R.C.P., D.O.M.S., F.R.C.S., Ophthalmic Consultant to the Government of W. Australia, 56 Hobbs St., Nedlands, Perth, W. Australia.

Honorary Associate Fellows

1955. Clement, Martin W., 6 Penn Center Plaza (4)
1955. Diemand, John A., President, Insurance Company of North America, 1600 Arch St. (2)

Necrological List

Resident Fellows	*Date of Election*	*Date of Death*
Bower, John O.	February 7, 1923	October 30, 1960
Elmer, Walter G.	February 3, 1904	May 17, 1960
Fiske, Frederick A.	April 4, 1945	July 10, 1960
Glover, Robert P.	January 6, 1954	February 1, 1961
Gouterman, Joseph I.	May 7, 1941	August 9, 1960
Hatfield, C. Alexander	January 9, 1946	December 31, 1960
Hewson, William	May 7, 1924	October 29, 1960
Hollingsworth, I. Pemberton P.	May 9, 1932	April 3, 1960
Jackson, Chevalier L.	May 9, 1932	January 13, 1961
Jacobs, Maurice S.	January 8, 1934	October 9, 1960
Kelly, George F. J.	January 7, 1935	October 6, 1960

Mullen, Carroll R.	January 7, 1935	February 1, 1961
Newcomet, William S.	January 4, 1905	September 9, 1960
Newton, Zachariah B.	October 12, 1938	May 18, 1960
Paschkis, Karl Ernst	April 5, 1944	January 27, 1961
Sommer, George N. J.	January 7, 1935	June 20, 1960
Weinstock, Horace L.	April 7, 1954	October 22, 1960
Williams, Carl	April 3, 1907	November 8, 1960
Non-Resident Fellows		
Clark, Jefferson H.	January 8, 1934	January 8, 1961
Menkin, Valy	October 4, 1949	December 13, 1960
Nisbet, Verner	March 5, 1941	January 5, 1961
Honorary Fellows		
McCarrison, Sir Robert	1922	May 18, 1960
Russell, Frederick Fuller	October 14, 1942	December 29, 1960

(*Suggested Form of Bequest*)

I hereby give, devise, and bequeath to the College of Physicians of Philadelphia, a charitable and educational association organized under the laws of the Commonwealth of Pennsylvania and the executive offices whereof are located in the City of Philadelphia, the sum of.....

a. which sum shall be used for the general purposes of said association;

b. which sum shall be added to and become a part of the general endowment fund of said association;

c. which sum shall be used by said association preferably for the following purposes:

Index to Volume 28

1960–1961

Aegerter, E. E., 225*
Africa, etiology of human liver cancer in, 61, health problems, 223, malnutrition, 195, medical education, 223
Akenside, Mark, 18th c. physician—poet, 46
Allen, G. S., 227*
Altman, A. A., 193
Alvarenga prize lecture: Merrill, J. P., 223
American medicine, two landmarks, 156
Anders lecture, Enders, J. F., 68
Anderson, O. E., 196
Appel, K. E., 52
Aronson, J. D., memoir of, 100
Arvan, D., Krumbhaar prize essay, 128

Balian, L. J., 193
Balistocky, M., 195
Barker, E. S., 194
Batterton, T. D., 193
Bellet, S., 194, 199, 217
Bequest, suggested form, 252
Billingham, R. E., 194
Bixby, E. W., Sr., memoir of, 57
Blady, J. V., 196
Blanco, G., 198
Blizzard, R. M., 193 223
Blood, coagulation, 103, lipids, 204, plasmin-plasminogen system, 205
Bluestone, N. R., Perkins prize essay, 135
Bockus, H. L., 225*
Boland, H. C., 202
Bone, marrow, 214, pulmonary osteoarthropathy, 202
Boucot, K. R., 194, 224*
Brest, A. N., 211
Brodey, R. S., 202
Brody, H., 224*
Brown, C. L., memoir of, 104
Broyles, E. N., 196
Bucher, R. M., 224*
Burns, healing visualization of, 1
Burnett, W. E., 225*

Cadbury, W. W., memoir of, 144
Cancer, liver, 61, cyclophosphamide therapy, 197, larynx, 196, lung, 219, paranasal sinuses, 195
Cannon, E. J., 195
Cantarow, A., 224*
Central nervous system, obscure diseases, 193, delirium tremens, 209, hemorrhage, 221, respiratory center, 199
Chirico, A. M., 225, 226*
Chlorothiazide, therapy of hypertension, 211
Cholecystitis, chronic, 193, diagnosis, 207
Chouké lecture, Denny-Brown, D., 14
Clark, D. A., 196
Coates, G. M., memoir of, 147
Coggins, P. F., III, 197
Collections, College: annual report, 188
College of Physicians of Phila.: Adm. staff, 227; Collections (ann. rep.), 188; Committees, 224; Fellows, 228; Inaugural remarks (Durant), 154; Lectures (1960), 223; Library (ann. rep.); 179; Mütter Museum (ann. rep.), 188; Officers, 224; President's address (Rhoads), 149; Sections, (officers), 226, (programs and abstracts), 193; Treasurer's rep., 175
Community, health interests, 141, hospital, 196
Conway, C. F., Jr., Perkins prize essay, 38
Cooper, D. A., 223*
Cowan, T. H., 195
Craig, F. A., memoir of, 54
Crane, A. R., 190, 224*
Cunningham, J. D., 196
Cyclophosphamide, therapy in malignancy, 197

Daly, J. W., 196
Davidson, W., 209
Declomycin, ocular penetration, 195
Dehne, T. L., 226*
Delirium tremens, fatalities, 209
Denny-Brown, D., Chouké lecture, 14
Diabetes mellitus, retinopathy, 195
Dietrich, H. J., Jr., 46, 226*
Di George, A. M., 213
Diuretics, comparative bioassay, 203
Dlin, B., 211
Dreifus, L. S., 216
Dunlap, E. A., 195
Durant, T. M., 104, 154, 194, 224*, 226*
Dyskinesia, biliary, 220

Ear, hearing loss, 196, pathology, 196, surgery, 196
EDTA, disodium, use in peripheral vascular disease, 218
Ehrich, W. E., 193, 225*
Eisman, S. H., 197
Ellis, R. A., 195
Elsom, K. O., 196

* Refers to the list of College officers, committees, sections, and administrative staff.

Enders, J. F., Anders lecture, 68
English, O. S., 106
Enzymes, use in therapy, 30, serum in myocardial infarction, 213
Eye, diabetes, 195, nevus, 195, malignancy, 195, nutrition, 195, optic chiasm, 195, strabismus, 195, surgery, 195

Fallot, tetralogy of, 194
Farrar, G. E., Jr., 194, 224*
Fat, effect of diet on coronary and pulmonary circulations, 204
Fay, M. S., 167
Feinberg, L., 213
Fellows, list of, 228
Fischer, H. K., 211
Fitz-Hugh, T., Jr., 225*, 226*
Flick, J. B., 54
Fowler, E. P., Jr., 196
Fraley, F., memoir of, 58
Frayer, W. C., 195
Fuchs, M., 203
Furgiuele, F. P., 195

Galilee, health education center, 135
Gallbladder, cholecystitis, 207, dyskinesia, 220
Garron, L. K., 195
Gates, Mrs. T. F., 223
Gettes, B. C., 195
Gibbon, J. H., Jr., 224*
Gill, R. J., 226*
Glycogen, storage disease, 199
Goldberg, M., 210
Goldburgh, H. L., 225*
Goldstein, F., 201, 220
Goodman, E. L., 193
Gout, urate crystals in synovial fluid, 209
Grant, F. C., 225*, 226*
Grotzinger, P. J., 224*, 225*
Grove, D. D., 224*
Guanethidine, use in hypertension, 196

Hafkenschiel, J. H., 193
Hagner, S. B., 212
Handler, J. S., 210
Hanlon, J. J., 226*
Harbert, F., 195, 196
Harkins, H. P., 195
Harley, R. D., 195
Harwick, R. D., 195
Hatfield lecture, Tillett, W. S., 30
Haupt, G. J., 193
Healing of burns, cellular events, 1
Health, guide, 94, education, 135, community, 141, center, 196
Heart, artificial pacemaker, 217, congenital disease, 194, coronary artery disease, 211, glycogen storage disease, 199, hypertension, 211, infarction, 211, mitral valve surgery, 198
Hemorrhage, intracranial surgical treatment, 221
Hitchens lecture, Sodeman, W. A., 223
Hitschler, W. J., 226*
Hodes, P. J., 225*
Hoffman, F. H., 196
Hollander, J. L., 209
Holling, H. E., 202
Hollingsworth, I. P. P., memoir of, 146
Hope, J. W., 193
Hormone, thyroid, 219
Hospital, health center, 196
Hostelley, W. V., 196
Housel, E. L., 196
Howard, J. M., 224*, 226*
Huber, J. F., 187, 224*
Huth, E. J., 193
Hyman, H. L., 225*
Hypertension, drug therapy, 196, 216, pathology, 221

Inaugural Remarks, T. M. Durant, 154
Incunabula, census supplement, 191
Ingraham, N. R., Jr., 225*
Intestine, pneumatosis cystoides, 202
Ismelin, therapy in hypertension, 196
Israel, health education, 135

Jeffers, W. A., 225*
Jefferson, Thomas, epistle to, 94

Kelly, J. G., 196
Kern, R. A., 224, 225*
Kirby, C. K., 193
Kirschner, R. J., 195
Kitchell, J. R., 218
Kline, O. R., 226*
Koop, C. E., 225*
Kramer, S., 201
Kremer, D. N., memoir of, 173
Krewson, W. E., 3rd, 226*
Krumbhaar, E. B., prize essay (Arvan), 128, 224*
Kuo, P. T., 204

Lame, E. L., 207
Lang, O. E., 227*
Lansbury, J., 216
Larynx, sarcoma, 196, surgery, 196
Levy, H. A., 215
Lewis, G. C., Jr., 193
Likoff, W. L., 198, 216
Liver, cancer, 61
LoCicero, V., 141
Long, E. R., 100
Lubrow, M. K., 195
Lucchesi, P. F., 225*
Ludwig, G. D., 193
Lymphatic system, observations and reflections, 109

Machella, T. E., 224*, 225*
Mackmull, G., 225*

MacNeal, P. S., 226*
Maldia, G., 215
Manzoli, U., 213
Marden, P. A., 226*
Mayerson, H. S., Newbold lecture, 109
Mayock, R. L., 193
Mays, R. W., 226*
McCarthy, P. A., memoir of, 103
McCarty, D. J., 209
McCouch, E. A., 226*
McDaniel, W. B., 2d, 184, 191, 227*
McLaren, D. S., 195
Mead, Kate Hurd, lecture, Miller, G., 80
Measles, viral agent, 68
Medical Documentation Service, 184
Medicine, American landmarks, 156
Meltzer, L. E., 194
Memoirs
Aronson, J. D., 100
Bixby, E. W., Sr., 59
Brown, C. L., 104
Cadbury, W. W., 144
Coates, G. M., 147
Craig, F. A., 54
Fraley, F., 58
Hollingsworth, I. P. P., 146
Kremer, D. N., 173
McCarthy, P. A., 103
Miner, C. H., 164
Pearce, L., 167
Solis-Cohen, M., 171
Sommer, G. N. J., Sr., 174
Stadie, W. C., 50
Strecker, E. A., 52
Stroud, W. D., 169
Weiss, E., 106
Merrill, J. P., Alvarenga prize lecture, 223
Miller, G., Mead lecture, 80
Miller, M. M., 224*
Miller, T. G., 57, 224*, 225*
Miner, C. H., memoir of, 164
Mirsky, I. A., 223
Mishler, J. E., 195
Moore, J. A., 196
Morse, E. H., 183, 227*
Moyer, J. H., 203, 211
Mütter lectures, Steiner, 61, Blizzard (*vice* Wilkins), 223
Mütter Museum: annual report, 188, committee, 224*
Muller, O. F., 199, 217
Muscle, diseases of, 14, myocardium, 199
Mydriacyl, cycloplegia—mydriatic, 195
Myocardium, infarction, 216

Neilson, N., 216
Newbold lectures, Pomerat, C. M., 1; Mayerson, H. S., 109
Newell, F. W., 195
Newton, D., 195
New York Academy of Medicine, Section on Otolaryngology, 196
Nichols, H. T., 198
Nicholson, J. T., 58, 171
Nickel, pulmonary carcinogen, 219
Norris, C. M., 196
Norris, R. F., 224*
Nose, paranasal sinuses, 195

Olsen, A. K., 226*
Ophthalmological cases, 196
Ornsteen, A. M., 226*
Orteza, J. M., 195
Oslick, T., 216
Osteoarthropathy, pulmonary, 202

Pacemaker, internal cardiac (artificial), 217
Padis, N., 226*
Parker, A. P., 224*
Peale, C. W., guide to health (letter to Jefferson), 94
Pearce, L., memoir of, 167
Pendergrass, E. P., 225*
Penneys, R., 213
Penn. Assoc. of First Aid & Rescue Squads, 223
Penn. Public Health Assoc., 196
Perkins prize essay, (I) Conway, C. F., Jr., 38, (II) Bluestone, N. R., 135
Pettit, M. D., 225*
Pfeiffer, D. B., 225*
Philadelphia County Medical Society, Eye Section, 195; Laryngological Society, 196; Joint Meetings, 223; Strittmatter Award, 223
Philadelphia doctors in White House, 128
Philadelphia Laryngological Soc., 196
Physick, P. S., friendship with B. Rush, 195
Piersol, G. M., 164
Plasmin, human, 205
Plasminogen, human, 205
Pleasants, H., Jr., 146
Poliomyelitis, viruses of, 68
Polymyositis, and related muscular diseases, 14
Pomerat, C. M., Newbold lecture, 1
Potter, H. P., 193
President's address (Rhoads), 149
Pyridoxine, deficiency, in hyperthyroidism, 215

Quinacrine, inhibition of LE cell formation, 216

Radbill, S. X., 224*
Rauwolfia, therapy in hypertension, 210
Raydin, I. S., 174, 225*
Raydin, R. G., 197
Raventos, A., 196
Rhoads, J. E., 149, 224*, 225*
Roberts, B., 193, 225*
Robertson, H., 103
Robbins, R., 225*
Rodman, T., 199
Rogers, F. B., 94, 224*, 225*, 226*, 227*

Rooney, J. F., 196
Royster, H. A., 255*
Rupp, J., 194, 226*
Rush, B., friendship with P. S. Physick, 194
Russell, G. W., 212

Sandberg, H., 206
Schaeffer, J. P., 224, 226*
Schaffer, B., 202
Scheffey, L. C., 224*, 225*
Scheie, H. G., 226*
Schenck, H. P., 147
Schlezinger, N. S., 194
Schlosser, W. D., 196
Schnabel, T. G., 156, 173, 223, 224*
Schnabel, T. G., Jr., 225*, 226*
Schreader, C. J., 226*
Schreck, K. M., 225*
de Schweinitz lecture, 195
Scott, M., 221
Scott, S., 196
Seaman, D., 195
Sellers, A. M., 194
Sex differentiation, abnormalities of, 223
Sheldon, G. F., 194
Sheps, C. G., 196
Shipman, J. S., 226*
Shuman, C. R., 224*, 226*
Silcox, L. E., 195
Smith, A. T., 195
Snyder, G. G., 196
Sodeman, W. A., Hitchens lecture, 223, 225*
Solis-Cohen, M., memoir of, 171
Soloff, L. A., 194
Sommer, G. N. J., Sr., memoir of, 174
Spaeth, E. B., 226*
Stadie, W. C., memoir of, 50
Starr, I., 50, 225*
Steatorrhea, postgastrectomy, 201
Steiger, W. A., 141, 225*, 226*
Steinberg, A. J., 202
Steiner, P. E., Mütter lecture, 61
Stokes, S. E., 144
Stoloff, I. L., 214
Strecker, E. A., memoir of, 52
Strittmatter award, T. G. Schnabel, Sr., 223
Stroud, W. D., memoir of, 169
Strumia, M. M., 224*
Sturgis, S. B., 226*
Sunderman, F. W., 219
Sunderman, F. W., Jr., 219
Surgery, open-heart in mitral valve disease, 198, ocular, 195, ear-tympanoplastic, 196
Syndrome, Devic's 195, Gerstmann, 195, Wegener's, 195, Menière's 196
Szutka, A., 215

Tassman, I. S., 226*
Taussig, H. B., 194
Tavel, M. E., 209
Temple University, community health interests, 141
Therapy, use of enzymes, 30, chlorothiazide, 211, guanethidine, 196, ganglion-blocking agents in hypertension, 211, rauwolfia, 211
Thompson, C. M., 193, 226*
Tillett, W. S., Hatfield lecture, 30
Tissue transplantation, 223
Tobacco, smoking and lung cancer, 219
Tonsil, palatine, 196, malignancy, 196
Toole, J. F., 226*
Tranquilizers, use and abuse, 38
Transplantation of tissue, 223
Treasurer's report, 175
Tsitouris, G., 206
Tympanoplasty, current techniques, 196

Unicorn, in medical history, 80
Uricchio, J. F., 198

Vastine, J. H., 2nd, 178, 224*, 225*
Virus, infection in measles and poliomyelitis, 68

Wade, E. N., 188, 190, 227*
Walsh, F. B., de Schweinitz lecture, 195
Watts, H. F., 194
Weiss, E., memoir of, 106
West, J. W., 204
Whayne, T. F., 196, 225*
Whelan, G. L., 226*
Whereat, A. F., 204
White House, Philadelphia doctors in, 128
Wiggs, A. E., 195
Wilkins, R. M., Mütter lecture, 223
Willauer, G., 224*, 225*
Williams, J. C., 224*
Winters, W. L., Jr., 211
Wirts, C. W., 201
Wohl, M. G., 215
Wolferth, C. C., 169
Wood, F. C., 223, 226*
Wood, H. C., Jr., 226*

Ylvisaker, L. S., 226*

Zatuchni, J., 225*

Vol. 28, No. 1
(4th Series)

July
1960

TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Contents

Visualization of Cellular Events in the Healing of Burns (*Mary Scott Newbold Lecture LXXVIII*) . . . . . Charles M. Pomerat 1

The Nature of Polymyositis and Related Muscular Diseases (*Hira S. Chouké Lecture III*) . . . . . Derek Denny-Brown 14

The Use of Enzymes for Therapy (*Nathan Lewis Hatfield Lecture XLIV*) . . . . . William S. Tillett 30

Tranquilizers: Their Use and Abuse (*William Harvey Perkins Prize Essay I*) . . . . . Cyril F. Conway, Jr. 38

Mark Akenside: Eighteenth Century Physician-Poet
Herbert J. Dietrich, Jr. 46

Memoirs:

William C. Stadie (1886–1959) . . . . . Isaac Starr 50

Edward A. Strecker (1887–1959) . . . . . Kenneth E. Appel 52

Frank Ardary Craig (1876–1959) . . . . . John B. Flick 54

Edward Welles Bixby, Sr. (1887–1959) . . . . . T. Grier Miller 57

Frederick Fraley (1876–1959) . . . . . Jesse T. Nicholson 58

PUBLISHED AT BALTIMORE, MARYLAND

The College of Physicians of Philadelphia does not assume responsibility for statements or views expressed by contributors to the *Transactions & Studies*.

The communications pertinent to their respective fields are indexed in: *Biological Abstracts; Chemical Abstracts; Index Medicus*.

The Transactions & Studies of the College of Physicians of Philadelphia is published four times a year—July, October, January, April—at Baltimore, Maryland by the College of Physicians of Philadelphia.
Subscription, $5 a volume. Single copies, $1.25.
Publication Office: Mt Royal and Guilford Aves., Baltimore 2, Md. *Editorial Correspondence* should be addressed to: The Editor, College of Physicians of Philadelphia, 19 South 22nd Street, Philadelphia-3, Pa.
Second-class postage paid at Baltimore, Md.
Printed in U. S. A.

The College of Physicians of Philadelphia

Founded 1787

1960

President

Jonathan E. Rhoads

Vice-president

Thomas M. Durant

Secretary

Thomas E. Machella

Treasurer

Jacob H. Vastine, 2nd

Censors

Edward B. Krumbhaar

T. Grier Miller

T. G. Schnabel

Lewis C. Scheffey

Honorary Librarian

Richard A. Kern

Council

The forenamed; Ex-presidential councillors O. H. Perry Pepper and J. Parsons Schaeffer; the chairmen of the Standing Committees; and the following

elective councillors

Robert M. Bucher

L. Kraeer Ferguson

Carl C. Fischer

Hugh Montgomery

Alan P. Parker

George Willauer

Librarian

Elliott H. Morse

Curator of Library Historical Collections

W. B. McDaniel, 2d

Curator of the Mütter Museum and Custodian of the College Collections

Ella N. Wade

Clerk of the College

Olga E. Lang

Superintendent

George S. Allen

Honorary Director of the Department of Medical Arts

Samuel B. Sturgis

Honorary Legal Counsel

Eric A. McCouch

Committee on Publication

John M. Howard, *chairman*

Fred B. Rogers

Max M. Strumia

Editor of the Transactions & Studies

Fred B. Rogers

Preceding Number

Vol. 27, No. 4, April, 1960

Contents

The Increasing Value of Medical Care (President's Address) Jonathan E. Rhoads 147
The College of Physicians of Philadelphia in Historical Perspective Richard H. Shryock 150
William Harvey Perkins Prize in Preventive Medicine William A. Steiger 158
Dr. William Harvey Perkins—A Tribute . . . . . Heinrich Brieger 159
Supplemental Catalogue of Medical Medals, Badges, and Coins in the College of Physicians of Philadelphia . . . . . Ella N. Wade 161

Memoirs
DeForest Porter Willard (1884–1957) . . . . . Jesse T. Nicholson 188
Chevalier Jackson (1865–1958) . . . . . Louis H. Clerf 190
Adolph J. Creskoff (1908–1959) . . . . . Thomas Fitz-Hugh, Jr. 192
George Wilson (1888–1959) . . . . . Charles C. Wolferth 193
Isaac Sharpless (1911–1959) . . . . . Orville Horwitz 195
Joseph J. Toland, Jr. (1887–1959) . . . . . James F. O'Neill 198

Annual Reports
Treasurer, 200; Library, 204; Mütter Museum and College Collections, 213

Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine 215
List of College Lectures, 1959 224
Membership Lists of the Sections 225
Officers, Committees, Sections, and Administrative Staff of the College, 1960 231
List of the Fellows 235
Suggested Form of Bequest 259
Index to Volume 27 260

Vol. 28, No. 4
(4th Series)

INDEX NUMBER

April
1961

TRANSACTIONS & STUDIES

of the

College of Physicians of Philadelphia

Contents

Annual Report of the President.....Jonathan E. Rhoads 149
Inaugural Remarks.....Thomas M. Durant 154
Two Landmarks in American Medicine—Their Impact
Truman G. Schnabel 156

Memoirs

Charles Howard Miner (1868–1959)....George Morris Piersol 164
Louise Pearce (1885–1959).....Marion S. Fay 167
William Daniel Stroud (1891–1959).....Charles C. Wolferth 169
Myer Solis-Cohen (1877–1960).....Jesse T. Nicholson 171
David Nathaniel Kremer (1890–1960).....Truman G. Schnabel 173
George N. J. Sommer, Sr. (1874–1960).....I. S. Ravdin 174

Annual Reports

Treasurer, 175; Library, 179; Mütter Museum and College Collections, 188.

Census of Incunabula in the College Library, Supplement I, 1960.... 191
Transactions of the Sections: Programs, and Abstracts from the Section on General Medicine..... 193
List of College Lectures, 1960..... 223
Officers, Committees, Sections, and Administrative Staff of the College, 1961..... 224
List of Fellows..... 228
Suggested Form of Bequest..... 252
Index to Volume 28..... 253

PUBLISHED AT BALTIMORE, MARYLAND

The College of Physicians of Philadelphia does not assume responsibility for statements or views expressed by contributors to the *Transactions & Studies*.

The communications pertinent to their respective fields are indexed in: *Biological Abstracts; Chemical Abstracts; Index Medicus*.

The Transactions & Studies of the College of Physicians of Philadelphia is published four times a year—July, October, January, April—at Baltimore, Maryland by the College of Physicians of Philadelphia.
Subscription, $5 a volume. Single copies, $1.25.
Publication Office: Mt Royal and Guilford Aves., Baltimore 2, Md. *Editorial Correspondence* should be addressed to: The Editor, College of Physicians of Philadelphia, 19 South 22nd Street, Philadelphia-3, Pa.
Second-class postage paid at Baltimore, Md
Printed in U. S. A

The College of Physicians of Philadelphia

Founded 1787

1961

President

Thomas M. Durant

Vice-president

John H. Gibbon, Jr.

Secretary

Thomas E. Machella

Treasurer

Jacob H. Vastine, 2nd

Censors

Edward B. Krumbhaar

T. Grier Miller

T. G. Schnabel

Lewis C. Scheffey

Honorary Librarian

Richard A. Kern

Council

The forenamed; Ex-presidential councillors O. H. Perry Pepper and J. Parsons Schaeffer; the chairmen of the Standing Committees; and the following

ELECTIVE COUNCILLORS

Robert M. Bucher

L. Kraeer Ferguson

Carl C. Fischer

Hugh Montgomery

Merle M. Miller

John C. Williams

Librarian

Elliott H. Morse

Curator of Library Historical Collections

W. B. McDaniel, 2d

Curator of the Mütter Museum and Custodian of the College Collections

Ella N. Wade

Clerk of the College

Olga E. Lang

Superintendent

George S. Allen

Honorary Director of the Department of Medical Arts

Samuel B. Sturgis

Honorary Legal Counsel

Eric A. McCouch

Committee on Publication

John M. Howard, *chairman*

Fred B. Rogers

Max M. Strumia

Editor of the Transactions & Studies

Fred B. Rogers

Preceding Number

Vol. 28, No. 3, January, 1961

Contents

Observations and Reflections on the Lymphatic System (*Mary Scott Newbold Lecture LXXX*) . . . . . H. S. Mayerson 109
Philadelphia Doctors in the White House (*Edward Bell Krumbhaar Prize Essay III*) . . . . . Dean Arvan 128
Observations of a Pilot "Health Education Center" in a New-Immigrant Town in the Upper Galilee (*William Harvey Perkins Prize Essay II*) . . . . . Naomi R. Bluestone 135
Community Health Interests of Temple University Medical Center
Victor J. LoCicero and William A. Steiger 141

Memoirs:

William Warder Cadbury (1877–1959) . . . . . S. Emlen Stokes 144
Israel Pemberton Pleasants Hollingsworth (1880–1960)
Henry Pleasants, Jr. 146
George Morrison Coates (1874–1960) . . . . . Harry P. Schenck 147

LIBRARY OF THE
COLLEGE OF PHYSICIANS
OF PHILADELPHIA

This Book is due on the last date stamped below. No further preliminary notice will be sent. Requests for renewals must be made on or before the date of expiration.

DUE	DUE
JAN 31 1962	
SEP 20 1962	
[illegible] 1963	
[illegible] 1964	

A fine of twenty-five cents will be charged for each week or fraction of a week the book is retained without the Library's authorization.